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A.M.A. JOURNAL OF

DISEASES OF CHILDREN

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TABLE OF CONTENTS

VOLUME 94 SEPTEMBER 1957 NUMBER 3

ORIGINAL ARTICLES

PAGE

Experiences with Chickenpox in Patients with Hematologic Disease Receiving Cortisone
Warren W. Nichols, M.D., Philadelphia 219

The Dietary Phenylalanine Requirements and Tolerances of Phenylketonuric Patients
Richmond S. Paine, M.D., and David Y. Y. Hsia, M.D., Boston, with the Technical Assistance of Hsio-Hsuan Hsia, A.B., and Kathleen Driscoll, B.A. 224

Pentylenetetrazol (Metrazol) in Mental Deficiency
H. H. Berman, M.D.; M. Lazar, M.D.; O. Noe, M.D., and H. Schiller, M.D., Staten Island, N. Y 231

Moniliasis in Pediatrics
Bohdan Dobiaz, M.D., New York 234

Gastric Perforation in the Newborn Infant
Daniel J. Abramson, M.D., and M. James Folston, M.D., Washington, D. C. 252

Nursery School
Wilma Buckman, M.A., M.S.W.; Helen Gofman, M.D., and George H. Schade, M.D., San Francisco 258

A Longitudinal Study of the Babinski and Plantar Grasp Reflexes in Infancy
Harry E. Dietrich, M.D., Beverly Hills, Calif. 265

The Role of Hemophilus Influenzae in Respiratory Infections of Premature Infants
William D. Donald, M.D., and James W. Coker, M.D., Birmingham, Ala. 272

Meprobamate in the Treatment of Epilepsy of Children
Samuel Livingston, M.D., and Lydia Pauli, M.D., Baltimore 277

Acute Adrenal Insufficiency Due to Congenital Defect
H. E. MacMahon, M.D.; Richard Wagner, M.D., and David B. Weiner, M.D., Boston 282

Narcotic Withdrawal Reactions in the Newborn
Nina Steg, M.D., Boston 286

Simultaneous Occurrence of Mongolism and Leukemia
William Krivit, M.D., and Robert A. Good, Ph.D., M.D., Minneapolis 289

Use of Chlorpromazine in Two Hundred Seventy-Eight Mentally Deficient Patients
George Tarjan, M.D.; Vincent E. Lowery, M.D., and Stanley W. Wright, M.D., Pomona, Calif 294

PROGRESS IN PEDIATRICS

Hypocalcemic States in Infancy and Childhood
Donald Gribetz, M.D., New York 301

CASE REPORTS

Apparently Unilateral Polycystic Kidney
Victor Menashe, M.D., and D. R. Smith, M.B., Ch.B., Edwards Air Force Base, Calif. 313

Neonatal Hepatitis in One of Binovular Twins
Bennett Miller, M.D., Albuquerque, N. M. 318

Large Ovarian Cyst in a Newborn Infant
Major W. T. Tyson (MC); Major James M. Keegan (MC), and Col. David Gold (MC), U. S. A. F. 320

Cysts of the Vagina in the Newborn Infant
Harry J. Cohen, M.D.; Milton D. Klein, M.D., and Myron B. Lazer, M.D., New York 322

REGULAR DEPARTMENTS

Abstracts from Current Literature 325

News and Comment 352

Books:

Book Reviews 353

Books Received 357

A. M. A.
Journal of Diseases of Children

VOLUME 94 SEPTEMBER 1957 NUMBER 3

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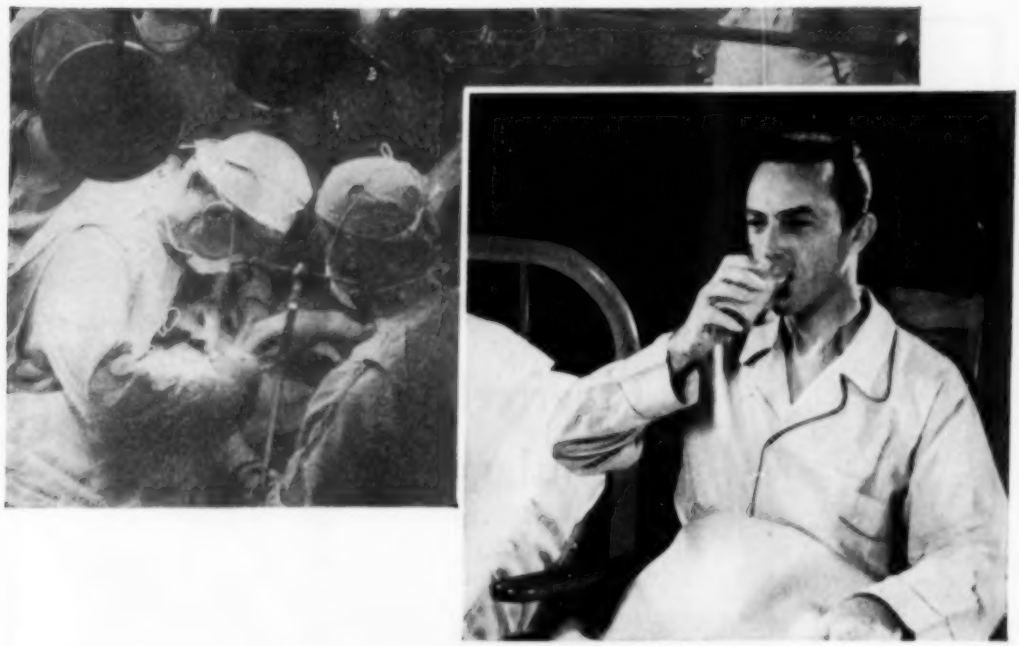

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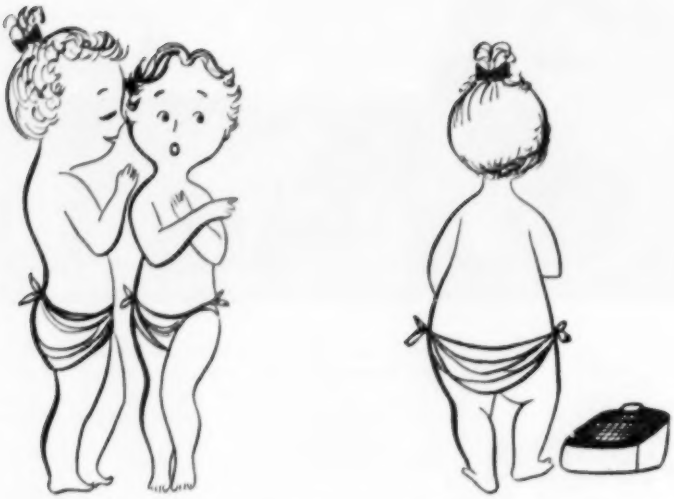

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Experiences with Chickenpox in Patients with Hematologic Disease Receiving Cortisone

WARREN W. NICHOLS, M.D., Philadelphia

Introduction

The enhancement of bacterial mycotic and viral proliferation by cortisone has been well established in clinical and experimental studies.[1-13] It is the purpose of this communication to present my experience when varicella was encountered in children with hematologic disorders while they were receiving cortisone or cortisone-like substances.[14] Three cases were studied, two with a basic diagnosis of leukemia and one with aplastic anemia. Of these three, two died during the acute illness.

Report of Cases

CASE 1.—A 3-year-old boy was diagnosed as having acute lymphocytic leukemia on Oct. 10, 1955. On Nov. 8, 1955, a diagnosis of florid chickenpox was made. At that time he was receiving 20 mg. of prednisone per day in divided doses (equivalent to 100 mg. cortisone) and amethopterin (4-amino-N^{10}-methyl-pteroylglutamic acid). Blood studies at the time the chickenpox was diagnosed revealed Hb., 10.2 gm.; WBC, 14,000, with 92% lymphocytes; platelets, 24,000. Prednisone was reduced to 15 mg. on the following day and to 10 mg. on the third day. Two days after onset of the varicella the patient died. The immediate cause of death appeared to be varicella and not the underlying disease process. No autopsy was obtained.

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Hematology Service, The Children's Hospital of Philadelphia. Formerly, Research Fellow in Hematology.

CASE 2.—A 2¼-year-old boy was diagnosed as having granulocytic leukemia on Oct. 6, 1952. On April 2, 1953, he was exposed to chickenpox. On April 12, 1953, he became ill, with a rash, irritability, and fever. The rash spread quickly, and severe abdominal pains developed. On April 16, 1953, he exhibited hematuria, and he was admitted to the hospital on April 17. At the time of admission his therapy consisted of cortisone, 25 mg. three times a day, and aminopterin once a day. Hemogram at this time revealed Hb., 9.6 gm.; RBC 2,900,000; WBC, 456,000, and platelets, 100,000. His course was rapidly downhill, and he died on the day of admission. No autopsy was obtained. The cause of death was obscure, but severe varicella appeared to have been a major contributing factor.

CASE 3.—A 5-year-old boy had a diagnosis of aplastic anemia made on March 15, 1956. He was in the hospital constantly from that time until April 20, 1956, when chickenpox developed. At that time he was receiving cortisone, 100 mg. per day in divided doses. Cortisone was reduced to 12.5 mg. b. i. d. when the diagnosis of chickenpox became evident. This illness was mild, and the lesions were dry on April 24, 1956, when cortisone was increased to 25 mg. three times a day. At the onset of varicella his blood count was Hb., 12 gm.; WBC, 3500, with a differential count of polymorphonuclear cells, 20%; eosinophils, 1%; lymphocytes, 79%, and 48,000 platelets. The platelet count fell to 2000 by April 25, 1956, on the reduced dose of cortisone.

Comment

A broad spectrum of side-effects and complications have been observed in patients receiving cortisone and corticotropin (ACTH).[15,16] Confusion often develops in attempting to classify which manifestations

are a direct expression of the underlying disease and those which appear to be related to steroid therapy. The treatment of complications associated with the use of these agents varies. When an infectious process develops during the administration of cortisone, or when cortisone is under consideration as a therapeutic adjunct in the treatment of an established infectious disease, the possibility of complications as well as the desired benefits must be considered. In infections which can be controlled by specific therapy, adrenal cortical hormone can be administered with safety if the need exists. However, it is known that these drugs can cause the enhancement of a variety of infectious agents. The mechanism of this enhancement is probably based on a variety of factors which involve the reticuloendothelial system, antibody-antigen interaction, and connective tissue and vascular permeability.[17-19] It appears that these steroids have little effect on previously acquired immunologic resistance. This fact in combination with inhibition of local inflammatory response is probably the basis for their successful use in conditions such as measles encephalitis.[20] In this instance the immunologic mechanism has been previously set in action and it is desirable to reduce the associated inflammation. In contrast, in varicella (or other infections lacking specific therapy) occurring in a patient who is already on steroids, the immune mechanism has not been started and is probably modified in association with inhibition of inflammation. This may predispose the patient to generalized spread of the disease and a fulminating course. Complete withdrawal of steroids after prolonged use in high dosage may conceivably induce adrenal insufficiency.

In this series the hematologic patients with severe chickenpox were thought to be severely ill because of general debility secondary to the underlying disease. However, other observers have noted similar occurrences in patients on cortisone with varied basic maladies.[9-11] Subsequently, a similar experience was met in a child with acute lymphocytic leukemia receiving 150 mg. of cortisone a day when she developed fever, dry cough, conjunctivitis, and Koplik's spots. A presumptive diagnosis of measles was made, and she was given γ-globulin and whole blood. Subsequent to this she developed clinical and x-ray evidence of pneumonitis (Fig. 1). She went rapidly downhill and died 15 days after onset of the acute symptoms, and, although she never developed a measles rash, autopsy revealed a giant-cell pneumonitis consistent with previous descriptions of measles pneumonitis (Figs. 2 and 3). Three other patients with classical measles while they were taking cortisone recovered uneventfully (summarized in the Table). Cortisone appeared to be largely responsible for the increased severity of the virus exanthemata, and treatment presented a difficult problem. Various

Fig. 1.—Chest x-ray of a 2¼-year-old girl receiving 150 mg. per day of cortisone orally for leukemia relapse. The bilateral pneumonitis followed the prodrome of measles, and autopsy revealed a giant-cell pneumonitis consistent with that seen in measles pneumonitis.

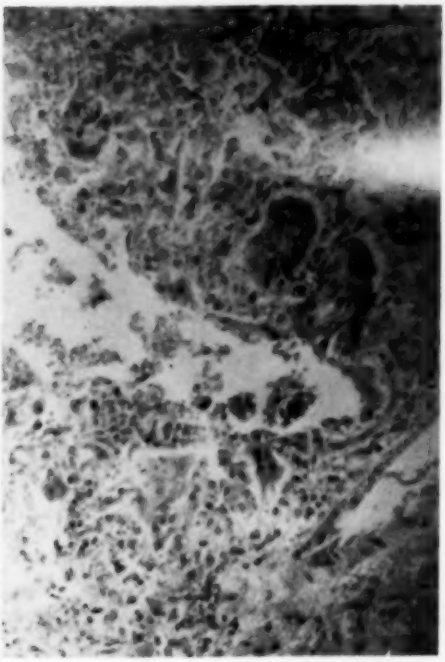

Fig. 2.—Photomicrograph of autopsy specimen of lung of the patient in Figure 1, showing giant-cell pneumonitis.

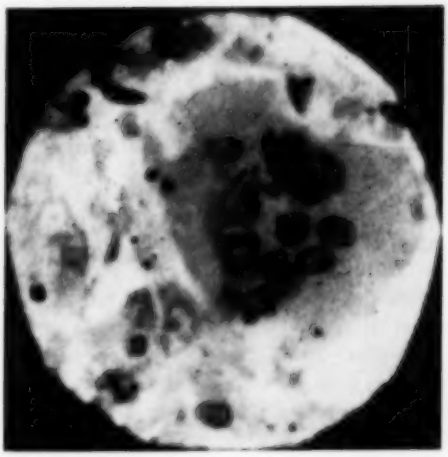

Fig. 3.—Photomicrograph of giant cell under high power from lung of the patient in Figure 1, who died with giant-cell pneumonitis.

consultants agreed that large doses of γ-globulin should be used for patients with measles and convalescent varicella serum for those with chickenpox. However, there was no agreement concerning management of cortisone therapy. Some felt that it should be increased, while others favored reduced dosage. Still others felt that it should be stopped completely.

Robinson et al.[21] studied bacterial infections induced in adrenalectomized animals treated with large doses of steroids. In this group cortisone was increased in some, stopped in others, and reduced in a third group. The optimal survival was in the group in which the cortisone was reduced.

All of our patients who had been taking 50 mg. of cortisone or less per day made an uneventful recovery when they contracted varicella and rubeola. The dosage, rather than the duration, of cortisone therapy seemed to be the determining factor (Table). It was decided that in patients developing measles or chickenpox while receiving high doses of cortisone or cortisone-like substances the doses would immediately be reduced to an estimated "physiologic stress level" of steroid. The dose initially used was 25 mg. of cortisone per day in

Dose and Duration of Cortisone Therapy Correlated with Exanthem and Outcome of Acute Exanthem

Case	Viral Exanthem	Antimetabolite	Cortisone Dose During Exanthem		Duration of Cortisone Therapy Prev. to Exanthem, Days	Complications	Results of Exanthem
			Drug	Mg./Day			
1	Chickenpox	Amethopterin	Prednisone	20*	30		Death
2	Chickenpox	Amethopterin	Cortisone	75	32	Abdominal pain, hematuria	Death
3	Chickenpox	None	Cortisone	25	30	None	Recovery
4	Presumptive measles	Amethopterin	Cortisone	150	39	Measles pneumonitis	Death
5	Measles	Aminopterin	Metacorten,	10†	33	None	Recovery
6	Measles	Aminopterin	Cortisone	50	21	None	Recovery
7	Measles	6-Mercaptopurine	Cortisone	25	40	None	Recovery

* Equivalent to 100 mg. of cortisone.
† Equivalent to 50 mg. of cortisone.

divided doses. Depending on the patient's course, this could be raised to 50 mg. per day. Many more cases are needed to determine the validity of such a suggested therapeutic regimen. Indeed, others have reported deaths on doses of cortisone as small as 25 mg. per day.[9]

Consideration should be given to the possibility of regular injections of γ-globulin at two-week intervals for prophylactic treatment of patients receiving large doses of cortisone. The possible production of antibodies against the regularly injected exogenous γ-globulin or whether the large doses of cortisone would negate this possibility are problems which are unanswered.

Mention should be made that cortisone may enhance the spread and recrudescence of dormant tuberculosis. This is illustrated by an 11-year-old girl who received intermittent cortisone for acute lymphocytic leukemia. It was known from the onset of her therapy that she had a positive old tuberculin test and possibly a Ghon complex on chest x-ray. When she died, autopsy revealed acute tuberculous lesions of the lung, liver, and spleen in addition to generalized petechial bleeding and leukemic infiltrations (Figs. 4 and 5). Another case with known family exposure to tuberculosis had suggestive clinical findings of tuberculosis and a reversal from negative to positive in the old tuberculin reaction, but autopsy was refused, and the diagnosis could never be substantiated.

Fig. 5.—Necropsy specimen of the liver showing tuberculous abscesses after intermittent cortisone therapy in the treatment of leukemia.

Fig. 4.—Necropsy specimen showing tuberculous abscesses of the spleen after intermittent cortisone therapy in the treatment of leukemia.

Perhaps this indicates that leukemia patients who have a positive tuberculin test or a strong family history should be given prophylactic isoniazid or a combination of isoniazid and streptomycin during cortisone therapy. Such therapy seems justified in leukemia, since there is little need to withhold antituberculous drugs for possible tuberculous infections in later life. The application of prophylactic isoniazid therapy in patients on cortisone with evidence of

old tuberculosis or a strong family history but nonfatal basic illnesses is an individual problem which cannot be limited by general rules of treatment.

Summary

Three cases of varicella in patients with hematologic disorders during cortisone therapy are presented. The increased severity of the exanthem in patients on cortisone is illustrated. Therapy currently employed consists of reducing the dosage of cortisone to a "physiologic stress level" and administering convalescent varicella serum.

A suggestion of increased severity of measles during therapy with large doses of cortisone is made. Therapy here is the same regarding cortisone, with the substitution of γ-globulin for convalescent varicella serum.

Prophylactic antituberculosis therapy during cortisone therapy in leukemic patients with a positive tuberculin test or strong family history of tuberculosis is proposed.

Drs. Irving J. Wolman, Bernard M. Wagner, and Alfred A. Bongiovanni assisted in the preparation of this manuscript. Miss Frederica M. Ballard helped in editing this work.

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REFERENCES

1. Pirart, J.: Granulie developpée chez un patient atteint de polisérosite rhumatismale traite à la cortisone, Acta clin. belg. 8:63, 1953; abstracted, Am. Rev. Tuberc. 68:93, 1953.

2. Harris-Jones, J. N., and Pein, N. K.: Disseminated Lupus Erythematosus Complicated by Miliary Tuberculosis During Cortisone Therapy, Lancet 2:115, 1952.

3. Antopol, W., and Quittner, H.: The Changing Pattern of Infectious Processes Under the Influence of Cortisone, J. Mt. Sinai Hosp. 19:91, 1952.

4. King, E. Q.; Johnson, J. B.; Batten, G. S., and Henry, W. L.: Tuberculosis Following Cortisone Therapy: Report of a Case of Rapidly Progressive Pulmonary Tuberculosis Following Cortisone Therapy for Rheumatoid Arthritis, J. A. M. A. 147:238, 1951.

5. Mach, R. S.: Indications, Contraindications and Dangers of Treatment with ACTH and Cortisone, Schweiz. med. Wchnschr. 81:155, 1951.

6. Walz, D. V.; Hasenclever, H. D., and McKee, A. P.: A Dual Human Infection with Candida Albicans and Cryptococcus Neoformans, Am. J. Clin. Path. 26:794, 1956.

7. Michael, M., Jr.: The Effect of Cortisone and ACTH on Bacterial Infections, South. M. J. 44:450, 1951.

8. Thomas, L.: Cortisone, ACTH and Infection, Bull. New York Acad. Med. 31:488, 1955.

9. Haggerty, R. J., and Eley, R. C.: Varicella and Cortisone, Pediatrics 18:160-162 (July) 1956.

10. Cheatham, W. J.; Weller, T. H.; Dolan, T. F., Jr., and Dower, J. C.: Varicella: Report of 2 Fatal Cases with Autopsy, Virus Isolation, and Serologic Studies, Am. J. Path. 32:1015, 1956.

11. Shee, J. C., and Fehrsen, P.: Reactivation of Varicella Virus by Cortisone Therapy, Brit. M. J. 2:82, 1953.

12. Schwartzman, G.: Enhancing Effect of Cortisone upon Poliomyelitis Infection (Strain MEF-1) in Hamsters and Mice, Proc. Soc. Exper. Biol. & Med. 75:835, 1950.

13. Kilbourne, E. D.: The Influence of Cortisone on Experimental Viral Infections, J. Immunol. 74:57, 1955.

14. Wolman, I. J.: Current Therapy of Childhood Leukemia, Quart. Rev. Pediat. 10:203, 1955.

15. Good, R. A.; Vernier, R. L., and Smith, R. T.: Serious Untoward Reactions to Cortisone and ACTH Therapy in Pediatric Practice: I. Pediatrics 19:95,; II., 272, 1957.

16. Smith, R. T., and Good, R. A.: Sequelae of Prednisone Treatment of Acute Rheumatic Fever, Clin. Res. Proc. 4:156, 1956.

17. Thomas, L.: Infectious Disease: Effects of Cortisone and Adrenocorticotropic Hormone on Infection, Ann. Rev. Med. 3:1, 1952.

18. Kass, E. H., and Finland, M.: Adrenocortical Hormones in Infection and Immunity, Ann. Rev. Microbiol. 7:361, 1953.

19. Selye, H.: Influence of STH, ACTH and Cortisone upon Resistance to Infection, Canad. M. A. J. 64:489, 1951.

20. Swanson, B. A.: Measles Meningoencephalitis, A. M. A. J. Dis. Child. 92:273, 1956.

21. Robinson, H. J.; Mason, R. C., and Smith, A. L.: Beneficial Effects of Cortisone on Survival of Rats Infected with D. Pneumoniae (20630), Proc. Soc. Exper. Biol. & Med. 84:312, 1953.

The Dietary Phenylalanine Requirements and Tolerances of Phenylketonuric Patients

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Introduction

Recently Rose and his co-workers [1] have shown that normal adults require a minimum of 0.8 to 1.1 gm. per day of L-phenylalanine, but that this figure may be reduced to about 0.3 gm. per day in the presence of excess tyrosine.[2] Snyderman and her associates [3] have estimated the minimal L-phenylalanine requirement of normal infants at 90 mg. per kilogram per day, but 60 mg. per kilogram per day sufficed in three of the six infants tested. Information has not been previously available as to the minimal or optimal phenylalanine intake of patients with phenylketonuria, and this becomes a point of some importance because of the low-phenylalanine diets currently being administered as a form of experimental treatment.[4-10] The body tissues of phenylketonuric patients contain phenylalanine in the same proportion as the tissues of normal persons,[11] and one must thus aim to provide sufficient dietary phenylalanine for protein-building without giving an excess which may result in elevation of the plasma phenylalanine level. The range of this requirement and its limits have been investigated in two patients by balance studies and will now be reported.

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Method

Two patients were utilized for the studies, and their histories and clinical state at the time of investigation were as follows.

Patient 1 was a 5½-month-old girl, 61 cm. in length and weighing 13 lb., with an estimated surface area of 0.3 square meters. She had a brother, aged 3 years, suffering from phenylketonuria, and a sister, aged 21 months, found to be normal. The patient's parents had believed her normal until the diagnosis of phenylketonuria was made, in the course of routine investigation of the older boy's sisters. Both parents and all three children are of small stature. The patient was the product of a normal pregnancy and delivery, with birth weight 6 lb. 6 oz. She was breast fed until one week prior to admission, but had been taking strained solid foods since the age of 3 months. She smiled at the age of 1 month, rolled over at 3 months, transferred objects from one hand to the other at 4 months, and was able to sit alone at the time of admission. Physical examination revealed an alert, small, but well-nourished blond brown-eyed girl. The head measured only 40 cm. in circumference, but examination was otherwise unremarkable. Her plasma phenylalanine level was 18.5 mg. per 100 cc., and the urine phenylpyruvate, 18.7 mg. per 24 hours. Routine laboratory studies of the blood and urine were otherwise normal.

Patient 2 was a 15-year-old boy, 55 in. tall and weighing 74 lb., with an estimated surface area of 1.15 square meters. He was the eldest of three children, the other two being normal. He sat alone at 1 year, walked at 2 years 11 months, and said a few words at 2½ years, but he later lost all speech. A diagnosis of phenylketonuria was made in early childhood, and the boy had been in a state institution since the age of 5 years 9 months. Two psychometric examinations at that institution resulted in estimates of his I. Q. at 19 and 28, respectively. On examination, the patient was a small, slender, but well-nourished boy with blue eyes and blond hair. His cranial vault appeared slightly small, although the head circumference was 52 cm. He sat quietly most of the day rocking back and forth on a chair, twisting or dangling a string or rag in front of his eyes. He showed

TABLE 1.—*Composition of Test Diet* for Patient 1, Aged Six Months, Weight Six Kilograms*

Period	Days, No.	Protein, Gm.							PA‡ Intake (Planned)	
		20 Gm. Protein Hydrolysate†	L-Tyrosine	DL-Threonine	L-Cystine	L-Tryptophane	L-PA‡	Total (Planned)	Mg./Day	Mg./Kg.
I	14	12.40	1.80	1.00	0.50	0.50	0	15.90	20	2.5
II	5	12.40	1.80	1.00	0.50	0.50	0.09	15.90	110	18.3
III	7	12.40	1.32	1.00	0.80	0.80	0.18	15.90	200	33.3
IV	4	12.40	1.23	1.00	0.50	0.50	0.27	15.90	290	48.3
V	4	12.40	1.14	1.00	0.50	0.50	0.36	15.90	380	63.3

† Containing 0.1% phenylalanine and 62% protein.
* The amounts of the following elements of the diet were the same in all periods: carbohydrate (Dextri-Maltose No. 2), 100 gm.; vegetable oil suspension (Lipomul, supplied by The Upjohn Company), 90 gm.; multiple-vitamin drops, 0.06 gm.; total Calories (planned), 854.
‡ PA, phenylalanine.

striking agitated hand posturing of the type usual in phenylketonuria. He had no speech but was usually continent of urine and feces if taken regularly to the toilet by attendants. General and neurological examinations were otherwise noncontributory except for markedly exaggerated knee jerks. For the preceding 10 months he had been taking a control (non-phenylalanine-deficient) protein hydrolysate diet, in connection with a controlled study of the effect of low-phenylalanine diets on patients with phenylketonuria.[10] Intractible refusal of the majority of the protein offered him resulted in low to moderate phenylalanine ingestion, and his plasma phenylalanine level had actually fallen to 4.9 mg. per 100 cc. prior to his being placed on minimal phenylalanine intake preparatory to beginning the balance study.

To initially reduce their plasma phenylalanine levels to normal values, both patients were given diets of which the entire protein component was supplied by a low-phenylalanine (0.1%) protein hydrolysate.* Details of the test diet for Patient 1 are given in Table 1. A considerable initial period (14 days) was required for her plasma phenylalanine to reach a normal level. The subsequent periods of the diet were planned for four days each, but some were longer because of difficulty in obtaining complete collections of urine and feces. A total protein intake of 16 gm. per day (weight 6 kg.) was planned, 12.5 gm. of this being supplied by the protein hydrolysate already mentioned and the remainder, by supplementary amino acids. The process of preparation of the hydrolysate by acid hydrolysis of casein followed by adsorption of phenylalanine on activated charcoal removes a certain amount of other amino acids. Supplementary amounts of tyrosine, threonine, cystine, and tryptophane were therefore added to insure against deficiency in these items and also to take advantage of the apparent phenylalanine-sparing effect of excess tyrosine.[8] In periods of the diet subsequent to Stage 1, phenylalanine was added in amounts planned to give 15, 30, 45, and 60 mg. per kilogram of body weight, the total protein intake being kept constant by subtracting a corresponding amount of tyrosine. All food and fluid intake was given as a single liquid formula preparation, the amount of this taken and refused each day being recorded. On the final day of each period the patient was placed on a metabolism bed to obtain a complete collection of stools and of urine, the latter being secured separately by an in-dwell-

* Ketonil, supplied by Merck & Co., Inc. This material contains 62% protein, or 10% nitrogen, and approximately 0.1% phenylalanine.

TABLE 2.—*Composition of Test Diet* for Patient 2, Aged Fifteen Years, Weight Thirty-Four Kilograms*

Period	Days, No.	Protein, Gm.							PA‡ Intake (Planned)	
		44 Gm. Protein Hydrolysate†	L-Tyrosine	DL-Threonine	L-Cystine	L-Tryptophane	L-PA‡	Total (Planned)	Mg./Day	Mg./Kg.
I	3	27.30	3.00	2.00	1.00	1.00	0	34.30	44	1.3
II	3	27.30	2.87	2.00	1.00	1.00	0.13	34.30	174	5.
III	3	27.30	2.70	2.00	1.00	1.00	0.30	34.30	344	10.
IV	3	27.30	2.53	2.00	1.00	1.00	0.47	34.30	514	15.
V	3	27.30	2.36	2.00	1.00	1.00	0.64	34.30	684	20.
VI	3	27.30	2.19	2.00	1.00	1.00	0.81	34.30	854	25.
VII	3	27.30	1.85	2.00	1.00	1.00	1.15	34.30	1,194	35.

* The amounts of the following elements of the diet were the same in all periods: vegetable oil suspension (Lipomul), 94 gm.; butter, 40 gm.; sucrose, 190 gm.; nitrogen-free baked goods (3 muffins, 140 Cal. each; 10 cookies, 70 Cal. each); 1 multiple-vitamin capsule; total Calories (planned), 2820.
† Containing 0.1% phenylalanine and 62% protein.
‡ PA, phenylalanine.

ing catheter. Total urine and stool nitrogen content and urine creatinine were determined by conventional methods.[13] Plasma and urine phenylalanine levels were determined on the last day of each period by a modification of the method of Udenfriend and Cooper,[14] and urine phenylpyruvate, by the method of Kropp and Lang.[15] Urine α-amino-nitrogen was determined by the method of Van Slyke.[16] All urine and stool collections were complete, or, if not, were repeated on subsequent days until complete, and so no correction factors were applied to the determinations. Nitrogen intake was calculated by dividing the known number of grams of protein ingested by 6.25.

Details of the diet planned for Patient 2 are given in Table 2. The protein intake was planned at 34 gm. daily (1.0 gm. per kilogram). Phenylalanine was added by a plan similar to that already outlined for Patient 1, to provide daily intakes of 5, 10, 15, 20, 25, and 35 mg. per kilogram in the consecutive stages of the diet. Nitrogen-free muffins and cookies were offered in considerable quantity to satisfy the patient's desire for bulk. If all were taken, the daily caloric intake would be 2800 calories, but the full number of muffins and cookies were not eaten. The diet provides 1700 calories if no baked goods are taken, but the patient's daily intake was never less than 2000 calories. Continuous consecutive 24-hour urine collections were made, with part of the specimen being unavoidably lost on approximately one-third of the days. Laboratory determinations on the urine were made as for Patient 1, the incomplete specimens then being corrected by a factor based on their creatinine content as compared with the mean creatinine content of all the complete specimens. A capsule of powdered carmine was fed at the beginning of each three-day period; the stool collection from the first appearance of carmine until its next detection thus being designated as corresponding to the proper dietary period. Blood and urine phenylalanine levels and urine phenylpyruvate were determined on the last day of each period.

Results

Data from the two patients are graphically represented in Figures 1 and 2. Plasma phenylalanine levels and urinary phenylalanine and phenylpyruvate excretion are presented in more detail in Table 3.

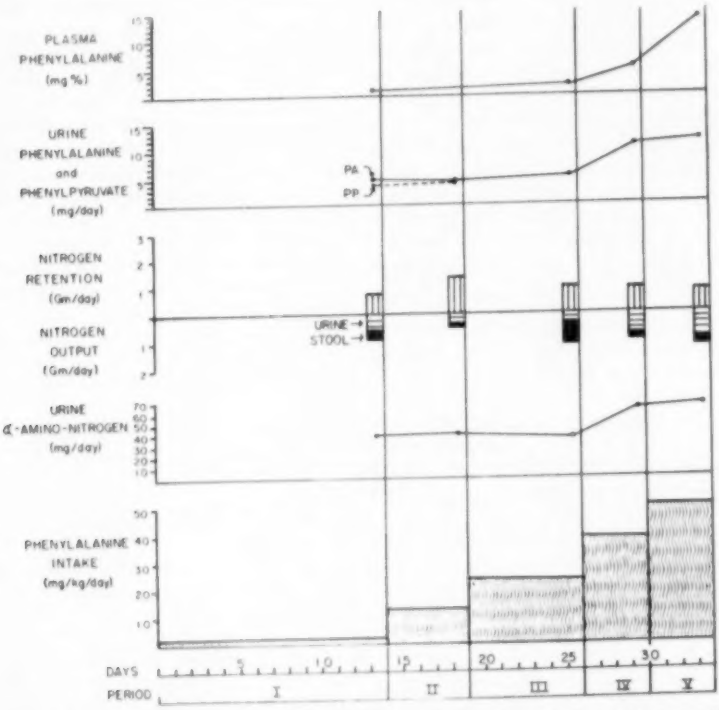

Fig. 1.—Studies on a 5½-month-old girl with phenylketonuria. Nitrogen balance estimation from collections on last day of Stage II is inaccurate because of the very small amount of feces passed on that day.

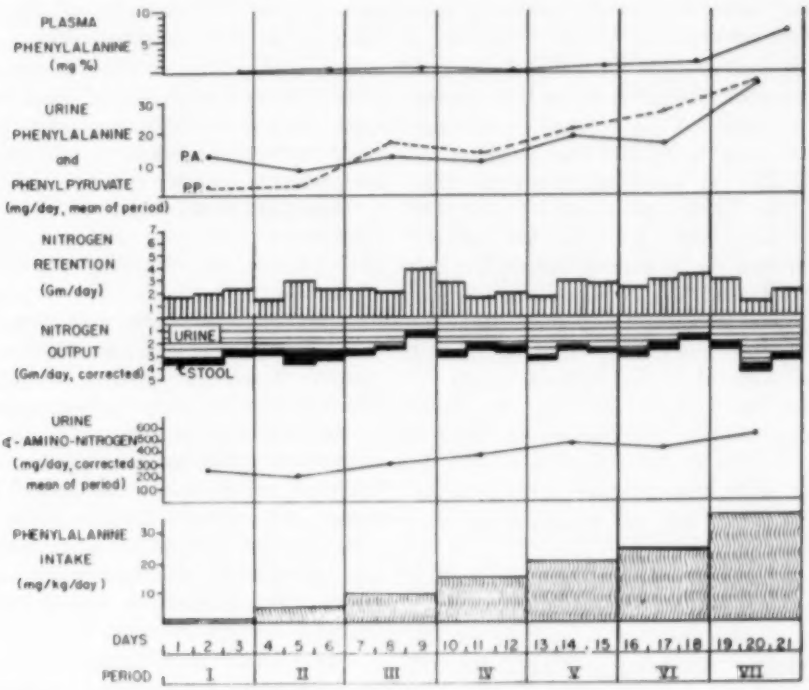
PLASMA PHENYLALANINE (mg %)
URINE PHENYLALANINE and PHENYLPYRUVATE (mg/day, mean of period)
PA
PP
NITROGEN RETENTION (Gm/day)
NITROGEN OUTPUT (Gm/day, corrected)
URINE
STOOL
URINE α-AMINO-NITROGEN (mg/day, corrected mean of period)
PHENYLALANINE INTAKE (mg/kg/day)
DAYS 1,2,3 4,5,6 7,8,9 10,11,12 13,14,15 16,17,18 19,20,21
PERIOD I II III IV V VI VII

Fig. 2.—Studies on a 15-year-old boy with phenylketonuria. In the case of incomplete urine collections, urinary nitrogen values are corrected by a factor equal to the mean of the creatinine content of all the complete 24-hour urine collections divided by the creatinine content of the individual incomplete specimen.

The top limit of normal for plasma phenylalanine in normal persons is probably 1.5 mg. per 100 cc.,[16] and the maximum phenylalanine intake tolerated without exceeding this figure would seem to be of the order of 20 mg. per kilogram in each patient. A sharp rise in urine phenylalanine and phenylpyruvate took place with Patient 2 at about the same level of intake. In Patient 1 the rise of urine phenylalanine began on

TABLE 3.—*Phenylalanine and Phenylpyruvate Data*

	Period	PA* Intake (Actual), Mg./Kg.	Plasma PA,† Mg./100 Cc.	Urine PA,† Mg./Day	Urine PP,*† Mg./Day
Patient 1 (age 6 mo.)	I	2.1	1.1	4.95	3.90
	II	13.0	..	4.32	4.14
	III	23.5	2.0	5.25	..
	IV	38.2	5.0	10.98	..
	V	50.0	13.7	11.88	..
Patient 2 (age 15 yr.)	I	1.3	0.2	12.9	2.6
	II	5.2	0.4	8.3	2.9
	III	9.9	0.6	12.2	17.3
	IV	15.3	0.2	11.2	12.0
	V	20.6	1.0	14.8	21.9
	VI	24.2	1.6	16.7	27.0
	VII	35.7	0.1	36.0	36.4

* PA, phenylalanine; PP, phenylpyruvate.
† Patient 1, values determined on last day of period (all urine collections complete); Patient 2, each value is the mean of three-day period (complete collections only).

TABLE 4.—*Urine Nitrogen Data*

	Period	PA* Intake (Actual), Mg./Kg.	N Intake (Actual),† Gm./Day	Total N in Urine,† Gm./Day	α-NH_2 in Urine,† Gm./Day
Patient 1 (age 6 mo.)	I	2.1	1.65	0.86	0.039
	II	13.0	1.80	0.38	0.040
	III	23.5	1.84	0.30	0.037
	IV	38.2	2.04	0.72	0.063
	V	50.0	2.00	0.89	0.066
Patient 2 (age 15 yr.)	I	1.3	5.49	2.9	0.26
	II	5.2	5.65	2.4	0.20
	III	9.9	5.20	2.3	0.30
	IV	15.3	5.20	2.5	0.27
	V	20.6	5.49	2.7	0.47
	VI	24.2	5.49	2.2	0.43
	VII	35.7	5.49	3.0	0.54

* PA, phenylalanine.
† Patient 1, value on last day of period (all urine collections complete); Patient 2, mean of three-day period (incomplete urine collections corrected individually by a factor equal to the mean creatinine content of all complete collections divided by the creatinine content of the incomplete collection involved).

a dietary intake between 25 and 35 mg. per kilogram per day.

Urine total nitrogen and α-amino-nitrogen determinations are given in Table 4. In the case of Patient 1 the total urine nitrogen showed a low point at a phenylalanine intake of 23.5 mg. per kilogram per day. Her urine α-amino-nitrogen remained stable until the same intake level and then showed a sharp rise. In the case of Patient 2, if one ignores Period VI, in which urine collections were incomplete and corrections uncertain, the total urinary nitrogen reached a low point at a phenylalanine intake of 10 mg. per kilogram per day, the urine α-amino-nitrogen also beginning to rise after that stage. Phenylpyruvate began to appear in the urine at a phenylalanine intake as low as 10 mg. per kilogram per day, however.

Figures 1 and 2 indicate that nitrogen retention occurred in both patients at all levels of phenylalanine intake, the amount of retention not being strikingly different at any point.

Comment

From the results obtained, there appears to be no minimal phenylalanine intake required to maintain a positive nitrogen balance, at least for short periods. There was, however, a minimal urinary nitrogen output at phenylalanine intakes of 23.5 mg. per kilogram in Patient 1 and 9.9 mg. per kilogram in Patient 2. The failure to demonstrate any negative nitrogen balances may be due to the shortness of the test periods (although it also failed to occur in the 14-day Period I for Patient 1), or it may indicate merely that it is extremely difficult to drive growing children into negative nitrogen balance if they are not acutely or chronically ill. In the studies of Snyderman and her associates,[3] the authors obtained a negative nitrogen balance on only one patient, and for only one study period. The imperfections of the data as to nitrogen balance are freely acknowledged, but the major points to be made by this report are based on the other determinations.

The urinary α-amino-nitrogen excretions of both patients were several times the accepted normal values.[17] This finding may be based on the feeding of amino acid mixtures, as opposed to complete proteins, and it is to be noted that in the studies of Holt, Pratt, Snyderman, and their colleagues,[3,18] on phenylalanine and threonine requirements of normal infants, the urinary α-amino-nitrogen excretions were also high. It is also to be noted that the supplementary tyrosine, threonine, cystine, and tryptophane added to the diets were probably in excess of the deficiency of these amino acids in the protein hydrolysate, and the excess may have been inevitably excreted as such in the urine. For example, 1.0 gm. of threonine added daily for Patient 1 is in excess of the total minimal threonine requirement of 60 mg. per kilogram per day, as estimated by Pratt and his colleagues.[18]

The maximal phenylalanine intake tolerated without rise in plasma phenylalanine levels appears to be of the order of 25 mg. per kilogram per day for both patients. In the case of Patient 2, however, this figure would amount to roughly 800 mg. per day, and it is much more doubtful that he would have been able to tolerate such an intake for a longer period. It has been our experience in the course of a one-year controlled study of the effect of low-phenylalanine diets in phenylketonuria [10] that it is impossible to reduce the plasma phenylalanine levels of adult and adolescent phenylketonurics to normal figures on a daily phenylalanine intake of more than 400 mg. per day.

The optimal phenylalanine intake can be estimated by correlations with urine and plasma phenylalanine, urine total nitrogen, and urine α-amino-nitrogen. The amounts would seem to be approximately 25 mg. per kilogram per day for Patient 1, at 6 months of age, and 5 to 15 mg. per kilogram per day for Patient 2, at 15 years of age. The former figure is considerably lower than the minimum of 60 and usual value of 90

mg. per kilogram per day for normal infants reported by Snyderman.[3] While this may suggest that the phenylalanine requirement of phenylketonurics is less than that of normal persons, the discrepancy may more plausibly be based on the fact that such a relative excess of tyrosine was not given in the diet administered by Snyderman and associates. Rose's[2] estimates of a minimal requirement of 300 mg. per day for adults in the presence of excess tyrosine would be 4 to 5 mg. per kilogram per day for a 70 kg. adult, a figure comparable to the lower end of the range for Patient 2. The fact that the latter is still growing may well account for his seemingly slightly greater needs. As applied to an adult with a surface area 1.75 square meters, Rose's figures would indicate a daily requirement of 170 mg. per square meter in the presence of excess dietary tyrosine, and 515 mg. per square meter without tyrosine excess. The range of 5 to 15 mg. per kilogram per day obtained for Patient 2 would correspond to 148 to 444 mg. per square meter per day, the extremes being comparable to the two figures obtained from Rose's data. In the case of Patient 1 the optimal phenylalanine intake of 25 mg. per kilogram per day is equal to 500 mg. per square meter per day, again comparable to the higher of Rose's estimates (in the absence of tyrosine excess). Since excess tyrosine was given to Patient 1, this may indicate that her need for dietary phenylalanine or substituted excess tyrosine is proportionately greater because of her younger age. The estimated optimal phenylalanine intake figures of 25 mg. per kilogram per day for infants and 10 mg. per kilogram per day for adolescents, with proportionate figures for intermediate ages, have been used as the basis for planning the diets of 22 phenylketonurics over a period of more than one year. This study will be reported separately, but it can be stated that nutritional difficulties have been encountered only in the frequency to be expected from the experience of others. Weight loss and malnutrition seem to result almost exclusively from periodic refusal of the patients to eat the unpalatable diet and not in the presence of reasonably complete ingestion of the full diet as planned.

Summary

Efforts have been made to determine the minimal, optimal, and maximal phenylalanine intakes of two patients with phenylketonuria, a 6-month-old girl and a 15-year-old boy.

A range of dietary phenylalanine intakes was offered, from as nearly 0 as was feasible to 50 mg. per kilogram per day in the case of the infant and 0 to 35 mg. per kilogram per day in the adolescent boy.

While positive nitrogen balance occurred at all levels of phenylalanine intake (at least for short periods), the optimal phenylalanine requirement was estimated on the basis of the point of minimal urinary total nitrogen and α-amino-nitrogen and the point at which a sharp rise took place in the previously stable plasma phenylalanine level and urine phenylalanine and phenylpyruvate excretion.

The optimal dietary phenylalanine levels for the infant of 6 months appeared to be approximately 25 mg. per kilogram per day, or 500 mg. per square meter per day. For the boy of 15, the possible range was 5 to 15 mg. per kilogram per day, or 150 to 450 mg. per square meter per day. The figures so determined have been used with success in planning the diets of 22 patients with phenylketonuria maintained on low-phenylalanine diets for a period of one year.

The figure quoted for the infant of 6 months is considerably lower than the requirement stated for normal infants by other investigators. The figures proposed for both the 6-month-old infant with phenylketonuria and for the boy of 15 years, however, are comparable to the extremes of the range of phenylalanine requirements reported by others for adults (170 mg. per square meter per day in the presence of excess tyrosine and 515 mg. per square meter per day without excess tyrosine).

Miss Sally O'Neill, Head Nurse of the Neurological Division of the Children's Medical Center, and all of the nursing and attendant staff of that ward, where these studies were carried out, cooperated in this work.

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REFERENCES

1. Rose, W. C.; Leach, B. E.; Coon, M. J., and Lambert, G. F.: The Amino Acid Requirements of Man: IX. The Phenylalanine Requirement, J. Biol. Chem. 213:913, 1955.

2. Rose, W. C., and Wixom, R. L.: The Amino Acid Requirements of Man: XIV. The Sparing Effect of Tyrosine on the Phenylalanine Requirement, J. Biol. Chem. 217:95, 1955.

3. Snyderman, S. E.; Pratt, E. L.; Cheung, M. W.; Norton, P.; Hansen, A. E., and Panos, T. C.: The Phenylalanine Requirement of the Normal Infant, J. Nutrition 56:253, 1955.

4. Bickel, H.; Gerrard, J., and Hickmans, E. M.: The Influence of Phenylalanine Intake on the Chemistry and Behaviour of a Phenylketonuric Child, Acta pædiat. 43:64, 1954.

5. Woolf, L. I.; Griffith, R., and Moncrieff, A.: Treatment of Phenylketonuria with a Diet Low in Phenylalanine, Brit. M. J. 1:57, 1955.

6. Armstrong, M. D., and Tyler, F. H.: Studies on Phenylketonuria: I. Restricted Phenylalanine Intake in Phenylketonuria, J. Clin. Invest. 34:565, 1955.

7. Braude, H.: Phenylketonuria: A Case Report in a European Child Treated with a Diet Low in Phenylalanine, South African M. J. 30:83, 1956.

8. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria: Clinical Observations in 3 Cases, J. A. M. A. 161:1628, 1956.

9. Blainey, J. D., and Gulliford, R.: Phenylalanine-Restricted Diets in the Treatment of Phenylketonuria, Arch. Dis. Childhood 31:452, 1956.

10. Hsia, D. Y. Y.; Paine, R. S.; Knox, W. E.; Mautner, H., and Quinn, K. V.: A One-Year Controlled Study of the Effect of Low-Phenylalanine Diets on Phenylketonuria, to be published.

11. Bloch, R. J.; Jervis, G. A.; Bolling, D., and Webb, M.: The Amino Acid Content of Tissue Protein of Normal and Phenylpyruvic Oligophrenic Individuals, J. Biol. Chem. 134:567, 1940.

12. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 12, Philadelphia, The Blakiston Company, 1947, pp. 814 and 839.

13. Udenfriend, S., and Cooper, J. R.: Assay of L-Phenylalanine as Phenylethylalanine After Enzymatic Decarboxylation: Application to Isotopic Study, J. Biol. Chem. 203:953, 1953.

14. Kropp, K., and Lang, K. A.: Eine colorimetrische Methode zur quantitativen Bestimmung der Phenylbrenztraubensäure im Harn, Klin. Wchnschr. 33:482, 1955.

15. Van Slyke, D. D.; MacFadyen, D. A., and Hamilton, P. B.: The Gasometric Determination of Amino Acids in Urine by the Ninhydrin-Carbon Dioxide Method, J. Biol. Chem. 150:251, 1953.

16. Hsia, D. Y. Y., and Driscoll, K. W.: Detection of the Heterozygous Carriers of Phenylketonuria, Lancet 2:1337, 1956.

17. Hsia, D. Y. Y., and Gellis, S. S.: Amino Acid Metabolism in Infectious Hepatitis, J. Clin. Invest. 33:1603, 1954.

18. Pratt, E. L.; Snyderman, S. E.; Cheung, M. W.; Norton, P.; Holt, L. E., Jr.; Hansen, A. E., and Panos, T. C.: The Threonine Requirement of the Normal Infant, J. Nutrition 56:231, 1955.

Pentylenetetrazol (Metrazol) in Mental Deficiency

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Introduction

Pentylenetetrazol (Metrazol) has been used as a respiratory stimulant for 30 years and as a convulsant for 20 years. The pharmacology and chemistry of the drug was described in 1937 by Giessen,[1] who gave a bibliography of the German literature up to that time. The use of pentylenetetrazol as a convulsant is well documented in the American literature. During the past five years, articles[2-24] have appeared on its use in senile and arteriosclerotic patients, with somewhat contradictory results; the majority felt that it in some way stimulated the patients, reducing the confusion, and caused a general feeling of well being. The beneficial effects have been attributed to the increased metabolism in the brain. Giessen pointed out that pentylenetetrazol increases the cerebral circulation and the amount of oxygen taken up. On the basis of this supposition, it was decided to try pentylenetetrazol on different groups of retarded children to determine whether or not it would have any beneficial effects on them.

Material

Three groups of children were used.

Group 1. Twenty-three children, 13 boys and 10 girls, diagnosed as having mental deficiency due to Mongolism, in the age range of 1-7 years. These children were all infantile, confined to cribs; none could sit or stand unsupported, and all were spoon- or bottle-fed. The age distribution was as follows:

Age, Yr.	Number
1-2	4
2-3	8
3-4	5
4-5	2
5-6	2
6-7	1
7-8	1

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Psychometric evaluation placed the children in the following groups:

Intelligence Quotient	Number
20-39	6
40-49	6
50-59	8
60-69	1
Over 70	2

Group 2. A group of 26 children, 17 boys and 9 girls, in the age range 4 to 11 years, who were all confined to cribs, were nonambulatory, and were the severest problems in a building housing approximately 250 nonambulatory children. The diagnostic distribution of these children was as follows:

Diagnosis	Number
Familial	2
Mongolism	1
Microcephalus	8
Hydrocephalus	2
Birth trauma	1
Trauma after birth	1
Undifferentiated	1
Due to infection (meningitis)	1
Congenital cerebral spastic infantile paraplegia	7
With other nervous disease	2

The age distribution in this group was as follows:

Age, Yr.	Number
4-5	2
5-6	3
6-7	3
7-8	9
8-9	5
9-10	1
10-11	1
11-12	2

The psychometric classification was as follows:

Intelligence Quotient	Number
Less than 20	15
20-29	9
30-39	1
60-70	1

Director (Dr. Berman), Assistant Director (Dr. Lazar), and Supervising Psychiatrists (Drs. Noe and Schiller), Willowbrook State School.

Group 3. A group of 72 girls in the age range 5 to 17 years, who were housed on one ward. The age distribution was as follows:

Age, Yr.	Number
5-6	1
7-8	1
8-9	1
9-10	8
10-11	10
11-12	16
12-13	14
13-14	11
14-15	2
15-16	5
16-17	2
17-18	1

The diagnostic distribution was as follows:

Diagnosis	Number
Familial	19
Mongolism	14
Hydrocephalus	2
Birth trauma	4
Epilepsy	1
Undifferentiated	28
Other types	3

The mental status distribution was as follows:

Intelligence Quotient	Number
0-19	11
20-29	19
30-39	17
40-49	9
50-59	8
60-69	6
Over 70	2

Procedure

No change was made in the routine of the child except the addition of pentylenetetrazol. In the first group, of Mongoloid children, the dose was ½ grain (32 mg.) t. i. d. In the second group, of severe problems, the initial dose was ½ grain t. i. d. and this was gradually increased to as much as 2 grains (130 mg.) t. i. d. In the third group, of ambulatory girls, the dosage was 1½ grains (97 mg.) t. i. d. Treatment was for a period of nine months. Before treatment was commenced, each child was evaluated on a rating scale consisting of 14 groups of abilities comprising 69 items. Rating was continued once monthly during treatment and for six months following treatment. Evaluations were made without reference to those made previously.

Results

No improvement was noted in any of the children which could be directly attributed to the use of pentylenetetrazol. In the youngest group of Mongoloids there was improvement noted consistent with the usual growth of these children within the period for which they were observed. In the two other groups no noticeable improvement could be attributed to pentylenetetrazol. Several complications occurred during the treatment, although no direct relationship could be found between the condition and the use of pentylenetetrazol. In the Mongoloid group, one child, who had never had convulsions, had one convulsive seizure during treatment. The children averaged a weight gain of 1.86 lb.; the weight of one child remained stationary; three children lost a slight amount; the remainder gained from less than 1 lb. to 6 lb. each. In the second group, of problem children, there were 19 who suffered from convulsive seizures. The pentylenetetrazol appeared to have no effect on any of these, except for one child who showed an increased number of convulsive seizures during treatment. The average gain of weight in this group was 2.03 lb. There were four children who lost weight and one whose weight remained stationary, the others gained from less than 1 lb. to 6 lb. each. In the ambulatory group, three children's treatments were discontinued because of disturbed behavior, which disappeared after the cessation of therapy. Three children died during the period on treatment, but no direct relationship was established.

Summary and Conclusion

Pentylenetetrazol (Metrazol) is a stimulant to brain metabolism and was experimentally administered to various groups of defective children to determine whether any change would occur.

Three different groups of children were used, and their behavioral patterns were noted on a chart at monthly intervals to determine changes. There was no significant change in the behavior of the children during therapy which could be attributed to the drug in the dosage administered.

The children were used as their own controls. They were placed on therapy for a

period of nine months and then observed for another period of six months to determine any changed rate of growth or behavior. No change in intellectual functioning was noted, and the physical and emotional progress noted was in keeping with the time interval.

Willowbrook State School (14).

REFERENCES

1. Giessen, F. H. in Handbuch der experimentellen Pharmakologie, Vol. 5, edited by A. Heffter, Berlin, Springer-Verlag, 1937, pp. 151-183.

2. Chesrow, E. J.; Giacobe, A. J., and Wosika, P. H.: Metrazol in Arteriosclerosis Associated with Senility, Geriatrics 6:319 (Sept.-Oct.) 1951.

3. Swenson, W., and Grimes, B. P.: Oral use of Metrazol in Senile Patients, Geriatrics 8:99 (Feb.) 1953.

4. Seidel, H.; Silver, A. A., and Nagel, H.: Effects of Metrazol and Nicotinamide on Psychic and Mental Disorders in the Geriatric Patient: A Preliminary Report, J. Am. Geriatric Soc. 1:280 (April) 1953.

5. Smigel, J. O.; Serhus, L. N., and Barmak, S.: Metrazol—Its Place in Geriatric Therapy, J. M. Soc. New Jersey 50:248 (June) 1955.

6. Jensen, E. H., and Leiser, R.: Oral Metrazol in Psychosis with Cerebral Arteriosclerosis, J. Michigan M. Soc. 52:734 (July) 1953.

7. Fong, T. C. C.: Oral Metrazol Therapy in Psychoses with Cerebral Arteriosclerosis, J. Am. Geriatrics Soc. 1:662 (Sept.) 1953.

8. Mead, S.: Mueller, E. E.; Mason, E. P.; Kheim, T., and Kountz, W. B.: A Study of the Effects of Oral Administration of Metrazol in Old Individuals, J. Gerontol. 8:472 (Oct.) 1953.

9. Levy, S.: Pharmacological Treatment of Aged Patients in a State Mental Hospital, J. A. M. A. 153:1260 (Dec. 5) 1953.

10. Lieberman, A. L.: Subconvulsive Intravenous Metrazol Therapy in Mental Patients: A Preliminary Report, Geriatrics 9:125 (March) 1954.

11. Andosca, J. B.: Effects of Pentylenetetrazol on Senile Patients: A Clinical Study, New England J. Med. 250:461 (March 18) 1954.

12. Callan, J. R., and Starnes, W. L.: The Analeptic Action of Oral Metrazol in Geriatric Practice, Dis. Nerv. System 15:121 (April) 1954.

13. Gross, M., and Finn, M. H. P.: Oral Metrazol Therapy in Psychotic Senile and Arteriosclerotic Patients, J. Am. Geriatrics Soc. 2:514 (Aug.) 1954.

14. Lieberman, A. L.; Schwartz, S. S., and Cooper, M.: Evaluation of Intravenous and Oral use of Metrazol in Hospitalized Arteriosclerotic Psychiatric Patients, Geriatrics 9:371 (Aug.) 1954.

15. Kirkpatrick, W. L.: The Relationship Between the State Mental Hospital and the General Practitioner, J. Louisiana M. Soc. 106:375 (Oct.) 1954.

16. Trevathan, R. D.: Convulsive Seizures During Oral Pentylenetetrazol Therapy, Geriatrics 9:489 (Oct.) 1954.

17. Sommer, R. J.: Oral Metrazol Therapy in Cerebral Arteriosclerosis, Illinois M. J. 106:323 (Nov.) 1954.

18. Lapinsohn, L. I.: Metrazol or Glutamic Acid in Treating Certain Mental Disorders? Pennsylvania M. J. 58:42 (Jan.) 1955.

19. Shapiro, R. P.: A Clinical Evaluation of Metrazol in Senile Women, Clin. Med. 2:29 (Jan.) 1955.

20. Hollister, L., and Fitzpatrick, W. F., Jr.: Oral Metrazol in the Psychoses Associated with Old Age, J. Am. Geriatric Soc. 3:197 (March) 1955.

21. Cohn, A. G., and Cohn, W. M.: Oral Metrazol Treatment of Senile and Arteriosclerotic Psychoses, New York J. Med. 55:1324 (May 1) 1955.

22. Sherwood, K. K.: Problems of the Aging: Conjoint Conference, University of Washington School of Medicine, Northwest Med. 54:480 (May) 1955.

23. Suter, W. B.: Oral Metrazol Therapy in Senility (a Preliminary Report), Dis. Nerv. System 16:211 (July) 1955.

24. Linden, M. E.; Courtney, D., and Howland, A. O.: Interdisciplinary Research in the Use of Oral Metrazol (Pentylenetetrazol) in the Emotional Disorders of the Aged, J. Am. Geriatric Society, to be published.

Moniliasis in Pediatrics

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1. Introduction

François Valleix,[1] a French pediatrician, wrote about thrush in 1838: "The succession of symptoms has not been studied as much as it should have been; the observers who are convinced that thrush means nothing more than a pseudomembraneous inflammation of the mouth have not been looking for signs of a more generalized infection." Valleix expressed this opinion in his voluminous book on the diseases of the newborn which was published one year before the fungus of thrush was discovered.[2] More than one-third of the book was devoted to thrush. The author reported in detail autopsy findings of 22 infants who died of systemic dissemination of thrush in a hospital within two and one-half months. More attention has been focused again on moniliasis recently partly because of accumulating reports of cases of this disease entity, especially following the use of antibiotics, and also because of the association of moniliasis with endocrine disturbances. Several reviews of the subject have been published,[3-9] some of them recently.[10-14]

The purpose of this paper is to correlate briefly the different disease forms of moniliasis in pediatrics and to present a few ideas about the pathogenicity of the causative agent of thrush.

2. Causative Agent

Moniliasis (candidiasis) is caused by yeast-like organisms of the genus Candida.[15,16] Candida albicans is most frequently responsible for human pathology, but other species (C. tropicalis,[17,18] C. pseudotropicalis,[19,20] C. krusei, [21,22] C. parapsilosis,[23-25] C. guilliermondi [26,27]) have been reported as causing human disease which at times terminated fatally.[17,19,20,24-27] The pathogenicity of different species of Candida in rabbits is not any reliable criterion for pathogenicity in human subjects.

As are many other micro-organisms, these fungi are facultative pathogens and are widely distributed among apparently normal, healthy persons. These carriers may remain symptomless for the lifetime. If the proper kind of physiological disturbance occurs in the host, however, the equilibrium is upset and latent infection evolves into overt disease.[28]

Bacterial micro-organisms, mainly streptococci and staphylococci, are often found together with Candida in cultures or in autopsy material from thrush lesions.[29-34] It is often difficult to decide which organism is primarily responsible for the lesion. Undoubtedly some lesions which are primarily caused by bacterial micro-organisms may become secondarily infected by Candida [35] and may eventually assume clinical characteristics of monilial lesions. In other instances lesions primarily due to the fungus may become infected with bacteria.[29]

3. Disease Forms

The disease forms range from the most benign cases, lasting a few days, comprising the majority, to acute disseminated cases, occurring mostly in infants and terminating fatally within days or weeks. Older children and adults may be afflicted with the most bizarre symptoms and may die after many years of chronic or recurring disease.

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A dissemination of the infection from the site of primary invasion (usually in the mouth) may occur directly, by continuity, but the fungus may spread further from secondary sites by the way of the blood stream and lymphatics.[36]

It has been shown that Candida may grow into blood vessels,[37] and that its yeast cells, forming at times inclusions in leukocytes,[38,39] may be carried in the blood stream. All potentialities for generalization are thus given. Heller examined sections of 38 organs (mouth, pharynx, esophagus, stomach, larynx, trachea, lungs) of 25 patients, mostly infants. The growth of Candida was limited to the epithelium in only 4 (12%) of 33 organs in which the fungus was found. In 12 organs (36.3%) Candida was growing in blood vessels.[40] Blood stream invasion probably occurs particularly in persons with a massive involvement of the gastrointestinal tract, mainly the esophagus.

Direct spread may cause lesions in the gastrointestinal and respiratory tract, possibly including the pleura[29] and diaphragm[29]; the vagina; the middle ear[29] and mastoid,[29] and, at least in some instances, the urinary tract. Hematogenous spread may result in dissemination into practically any organ. At the time when signs of dissemination are detected the primary lesions may or may not have disappeared. Absence of oral thrush in these diagnostically difficult cases, therefore, is not any evidence against the monilial etiology, the oral mucosa being only one, chronologically and by frequency usually the first, of many possible sites of infection.

The response of infants and young children to Candida infections differs in certain respects from that in older children and adults, similarly as, e. g., in tuberculosis. Hematogenous dissemination with a very acute, frequently fatal, course is more likely to develop in infants and young children than in adults. The character of skin lesions in the two age groups also differs considerably, as a rule. Cutaneous manifestations in infants are mostly superficial, are more widespread, and have a larger amount of inflammatory reaction, while those in older persons tend to be more localized and deeper. Alymphocytosis, a blood dyscrasia discussed later in this paper, has been reported in infants and very young children only. Endocrine disturbances may be seen with moniliasis in patients beyond infancy. Because of these differences, moniliasis in the two age groups will be dealt with in two separate chapters, although there is some overlapping between the two age groups.

4. Moniliasis in Infants

Moniliasis may start at any age from an endogenous or exogenous source, but the first appearance of the disease probably occurs more often during neonatal life or early infancy than at any other age. At times latent infection or clinical disease may remain present for years. The effects may be projected into adolescence and beyond. The symptoms, however, may, and usually do, disappear spontaneously or as a result of treatment at any point, especially before dissemination sets in.

A. Oral Cavity.—In the majority of cases clinical thrush probably remains limited to the oral cavity, which is the portal of entry in most infants. The average interval after birth for the development of oral thrush is eight to nine days.[5,36,41] Candida may be found, however, in the mouth of infants in the first days of life without necessarily causing clinical thrush later.[5] Some workers believe, however, that clinical thrush in infants always follows the finding of Candida in the mouth.[41]

The familiar white patches, at times with an underlying inflammatory reaction, are usually located on the buccal mucosa, on the tongue and gums (Figs. 1 and 2). Less frequently the soft palate, the fauces, the uvula, and the tonsils are covered, sometimes without any involvement of the buccal mucosa.[42] Isolated lesions on the tonsils yielding Candida and bacterial organisms have been reported in young infants.[30] The

mucous membranes of the entire oral cavity may be covered with confluent whitish, yellowish, or grayish pseudomembranes of thrush.

B. Gastrointestinal Tract.—The esophagus seems to be the most frequent site of monilial lesions in the gastrointestinal tract.[1,29,36,37,43-45] De Gavaller [46] found lesions caused by Candida in 72 (25%) of 288 autopsied newborn infants. In 36 (50%) of these 72 cases there was moniliasis of the esophagus. In another series, 22 of 28 cases of esophagitis in infancy were caused by thrush.[47] The whitish pseudomembrane usually stops abruptly a few millimeters above the cardia. The lesions sometimes consist of isolated patches similar to oral thrush. In extreme cases, masses of fungus growth may entirely obstruct the lumen of the esophagus.[48] Infants may regurgitate, vomit, and possibly aspirate [29] pieces of such fungus growth. Fatal bleeding from ulcerations of the esophagus with arrosions of the vessels has been reported.[49]

Lesions of the stomach [42,46,51-54] and intestines are not as common as those of the esophagus. Among 72 autopsied infants who revealed evidence of pathology due to Candida, de Gavaller [46] found lesions of the stomach in 3 (4.2%), those of the intestines in 4 (5.5%). Pseudomembranes are found in mild cases. Large white masses of fungus growth were removed from the ampulla of an infant.[55] Ulcerations of the small [46,50,51-56,57] and large [47,51,57] intestines, at times with perforation [51,56,57] and consecutive peritonitis,[51,57] have been reported. Some infants with intestinal involvement have loose stools, and the possibility of thrush etiology of diarrhea in infants with any evidence of moniliasis should be kept in mind.[1,10,51,53,56,58,59] Nineteen per cent of my 70 cases of cutaneous moniliasis had diarrhea. Eighty-seven per cent of 60 cases in which stools were examined had Candida in the feces. The stools became normal promptly in the majority after a course of treatment with nystatin alone.

C. Skin.—Superficial cutaneous moniliasis [60-64] is, with the exception of oral thrush, the commonest early symptom accessible to physical examination.

Most frequently lesions start around the anus, or on the prominences of the buttocks, spreading at times to the genital region and the inner and posterior aspects of the upper thighs and the lower abdomen, rarely to the lower back. In Bound's experience the perianal region was less frequently involved than the buttocks.[65] Similar lesions in the face may also appear. At times weeping intertriginous lesions are present around the neck, behind the ears, and in axillary regions. Rarely, the entire body may be covered. In such instances the clinical picture may resemble that of Leiner's erythrodermia desquamativa.[66-68]

The initial lesions are usually erythematous papules or tiny vesicles (Fig. 3) which soon tend to become confluent, forming large erythematous patches denuded of superficial epithelium, with a scaly periphery and heaped-up sharp borders of whitish detached epidermis (Fig. 4). Satellite lesions of the same character are generally present. In some cases intertriginous lesions are oozing. At times the initial lesions do not become confluent and the affected areas may be covered with small squamous patches resulting from rupture of the vesicles. A striking feature in almost all Negro infants in my series,[69] not described to my knowledge before, was a marked depigmentation of the lesions resembling achromia parasitaria (Fig. 5).[70,71] The erythema in Negroes was not as pronounced as in white infants. The depigmentation disappeared completely in all treated patients within several weeks.

Infants with extensive involvement of the skin may develop lesions of the scalp which are more often sharply delineated than diffuse, with drab-colored scales.[66,72] The lesions may be oozing, and some consecutive crusting may be present. Most infants develop a transient loss of hair, which is usually less pronounced than in tinea capitis (Fig. 6).

Vulvovaginitis, as may be expected, accompanies extensive cutaneous and gastrointestinal moniliasis at times.[47] Perlèche,[42] balanitis,[47] paronychia,[73] onychia,[74-75] conjunctivitis,[47] and blepharitis[42] may occur, although they appear to be relatively rare in infants. Some cases of urinary tract involvement may result from an ascending infection from the skin or vulva, although the majority seem to be hematogenous.

The skin in infants probably in most cases becomes infected from feces containing the fungus as a result of oral and successive gastrointestinal moniliasis. Several facts are in favor of this assumption: 1. All 40 infants less than 3 months old with cutaneous moniliasis in my series had feces positive for C. albicans. This is in accord with the findings of Ibrahim,[61] Epstein[5] and Mayer et al.[66] but not with those from Holzel's[76] small series. 2. The lesions usually start around the anus. 3. In some cases oral thrush can be seen at the onset of the dermatitis; in others, careful questioning or search of hospital records reveals its history. 4. In such cases there is usually a lapse of time between the onset of oral thrush and dermatitis in the diaper area. Several days are apparently needed for Candida to be carried from the oral cavity through the entire gastrointestinal tract and cause infestation of the feces.[5] 5. Relapses are often seen in cases in which topical treatment of the dermatitis is not accompanied by an attempt to treat gastrointestinal moniliasis.

Obviously, other ways of transmission are possible. Direct contamination of the skin during the passage through the birth canal might be one. The skin may be infected by a nurse's or mother's hands[65,76] or insufficiently sterilized diapers,[66] especially in cases in which Candida is not found in the feces. An infant sucking his fingers may cause skin lesions in the reach of his hands which are contaminated with Candida from his oral cavity.[36]

Contaminated urine might infect the skin. I saw a 2-year-old boy with C. albicans in the urine, balanoposthitis, and several lesions on the inner thighs and the abdomen (Fig. 7). Although I have not observed any young infant in whom such extension to the skin could have been suspected, this might be a possibility in infants as well, especially after antibiotic treatment. Ballowitz and Schäfer examined urine specimens of 142 infants and children who had received antibiotics. They found fungi in the urine in 16 of them. In a control series of 800 children without any previous antibiotic treatment no fungi were cultured from the urine.[77]

This dermatitis of the newborn seems to be rather common, especially in the lower economic group of the population. Bound found an incidence of almost 3% in the first 6 months of life.[65] A surprisingly high incidence of 35% in hospitalized infants less than one month old was reported from Germany recently.[13]

Clinical diagnosis can be made with considerable accuracy.[65] Many cases, however, are diagnosed as simple diaper rash, infantile eczema, or, at times, ringworm. Because of its apparent frequency cutaneous moniliasis should always be considered in differential diagnosis of diaper rash.[65,78]

Hematogenous spread to the skin was suspected in a newborn infant with atypical skin lesions and onychia which were noticed at the age of one day. Candida was cultured from widespread tiny white pustules surrounded by narrow erythematous areolas. Oral thrush was absent.[74]

D. Respiratory Tract.—Lesions of the pharynx, larynx, and trachea[40,47,79] have been reported in infants. They probably occur much less frequently than esophageal lesions. Tonsillitis[80] and laryngitis[40,45,81] caused by Candida may closely resemble diphtheria clinically. Adherent masses of fungus growth may be found on vocal cords,[40,82] or the entire larynx may be covered with a pseudomembrane.[42,79] Aphonia may accompany thrush laryngitis. Extensive laryngitis may necessitate a tracheotomy because of extreme dyspnea.[81]

A pseudomembrane may extend from the pharynx into the Eustachian tube.[42] Purulent otitis and mastoiditis [29,47] which were reported in infants with an extensive involvement of the esophagus and pharynx probably resulted from dissemination by continuity through the Eustachian tube.

A definite clinical diagnosis of bronchial and pulmonary moniliasis is difficult to establish, especially in infants. Although such lesions seem to be less common in infants than in older persons, pathological changes of the bronchi and lungs do accompany other symptoms of moniliasis in this age group at times, and Candida has been demonstrated in the lung on section and culture in several instances.[33,46,51,52,83,84] Schürmann [85] found Candida in pure culture in the lung and in the blood stream of a premature infant who died at the age of 2 days. History in this case and histologic appearance in others suggest possible hematogenous spread to the lung.

Most infants with mild oral, gastrointestinal, and cutaneous moniliasis are in a relatively good general condition. The course is usually benign, although it may become chronic. The temperature is either normal or slightly elevated. The total and differential white cell counts are usually within normal limits. Some itching may be present in infants with cutaneous lesions. Patients with pulmonary moniliasis may be dyspneic and febrile.

E. Systemic Moniliasis.—Systemic moniliasis, or Candida septicemia, results from dissemination by the way of blood stream or lymphatics. Lederer and Todd [29] believe that diagnostic difficulties in the living and at necropsy may be responsible for a significant number of cases of fatal moniliasis which remain undetected and unrecorded. According to these as well as other [80] authors, thrush may pass unrecognized at autopsy unless histological examination is undertaken, since, generally, there is a lack of specific macroscopic features to suggest the diagnosis of moniliasis.

Fig. 1.—Oral thrush of three weeks' duration in an infant. No therapeutic response to methylrosaniline chloride.

Fig. 2.—Extensive oral thrush with thick pseudomembranes. Accompanying bronchitis and diarrhea responded to oral administration of nystatin.

Fig. 3.—Early cutaneous moniliasis with papular and vesicular lesions. White patches in inguinal creases resemble oral thrush.

Fig. 4.—Typical cutaneous moniliasis several days after the onset. Note sharp borders of detached epidermis and satellite lesions.

Fig. 5.—Depigmentation in a Negro infant with cutaneous moniliasis. Note satellite lesions and loss of pigment in axillary regions, face, and neck.

Fig. 6.—Vesiculopustular scalp lesions yielding Candida with partial loss of hair in an infant with oral and perianal moniliasis.

Fig. 7.—Papulovesicular crusted lesions yielding Candida in boy with urine cultures positive for Candida. History of systemic antibiotic treatment.

Fig. 8.—Circinate crusted papulovesicular lesions in a 7-year-old boy. Skin scrapings positive for Candida. Two siblings had oral, vaginal, and cutaneous moniliasis.

Fig. 9.—Retroauricular weeping intertriginous lesion. Note peripheral scaling and crusting and small satellite lesions. Culture was positive for Candida.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

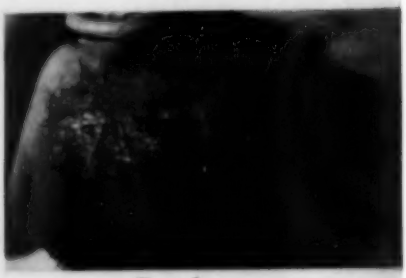

Figure 6

Figure 7

Figure 8

Figure 9

Figure 10

Figure 11

Figure 12

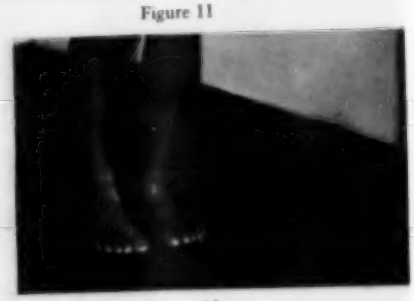

Figure 13

Figure 14

Figure 15

Figure 16

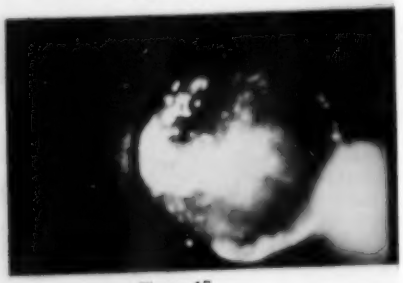

Figure 17

Figure 18

Plenert [13] maintains that diagnosis of systemic moniliasis at autopsy can be established only when Candida is found in the liver, brain, or parenchyma of the kidney. A list of several other organs mentioned later in this section may be added to this statement. Laboratory diagnosis in the living is equally difficult. Plenert [13] postulates positive blood cultures; Vince and Csilag,[86] positive cultures of specimens in which Candida can never be found under normal circumstances, namely, the cerebrospinal fluid, blood, or catheterized urine. The authors caution that one negative culture does not exclude the diagnosis. As in suspected systemic bacterial disease, cultures should be repeated several times.

Certain clinical features, however, may suggest the diagnosis. A review of the literature reveals a high incidence of very uniform symptoms in infants who either died of systemic moniliasis or recovered and were shown to have had an extensive monilial infection.[1,29,47,49,58,83,88-90] Outstanding signs in this syndrome are anorexia, severe postprandial vomiting, progressive wasting, diarrhea with resulting dehydration, and toxic appearance, at times with pallor, cyanosis, and sudden collapse. The temperature is usually normal, or a moderate, rarely high, fever [52] may be present. Occasionally there are periods of hypothermia. Presence of blood in the vomitus,[29,47,49] melena,[47,49,56] and projectile vomiting simulating pyloric stenosis[29,47] have also been reported. As have several other observers,[40,52,53,80,91-95] I have noted hepatosplenomegaly or splenomegaly without any other obvious reason at some time, or constantly, in the course of extensive moniliasis in infants and children.

Since probably many cases of systemic moniliasis in infants are accompanied or preceded by a more or less extensive cutaneous moniliasis,[1,42,46,53,73,80,89,90,96] the knowledge of its symptomatology is a valuable diagnostic aid in such cases. The presence or history of oral thrush should also be looked for, as well as maternal vaginitis and possible predisposing factors for moniliasis.

The course of systemic moniliasis in this age group is usually more acute than that

Fig. 10.—Round weeping plaque delineated by a border of vesiculopustules in a 2-year-old boy. Candida was present in the skin scrapings, mouth, and feces.

Fig. 11.—Chronic scattered dry scaly lesions yielding Candida.

Fig. 12.—Chronic discrete circumscribed scaly lesions of same patient as in Figure 8. Culture positive for Candida.

Fig. 13.—Eczematoid lesions yielding Candida in a 7-year-old boy with a long-standing history of oral and cutaneous moniliasis.

Fig. 14.—Perlèche of a mother of two children with widespread moniliasis.

Fig. 15.—Monilial granuloma of arms and legs. Heavy growth of Candida in pus from multiple abscesses.

Fig. 16. Recurring crops of papules with superficial scaling, probably candidids. The lesions appeared about three weeks after the onset of the first symptoms of oral, cutaneous, and gastrointestinal moniliasis. No organisms were cultured from these widely scattered papules, which had disappeared after oral application of nystatin.

Fig. 17.—Candida vaginitis.

Fig. 18.—Papular lesions yielding Candida in the same mother as in Figure 14.

of disseminated Candida infections in older children and is often fatal.

Abscesses of various sizes, mainly miliary abscesses, have been found in the kidney,[29,46,58,97-99] brain,[58,89] spleen,[42,98] liver,[46] subcutaneous tissue,[97,100] myocardium,[58,101,102] diaphragm,[58] and other muscles.[58] Peritonitis,[51,57] endocarditis,[101,102] pericarditis,[101] pleurisy,[101] and meningitis[32,58,103,104] have also been reported, as well as pyelitis,[83,97] cystitis,[55] and infections of the ureters.[55] Several organs are usually affected in an infant.

F. Alymphocytosis.—An unusual blood dyscrasia has been described in infants with widespread Candida infections. The lymphocytes may completely or almost completely disappear from the peripheral blood; the lymphoid tissue all over the body may become atrophic or necrotic. Disappearance or ulceration of Peyer's plaques has been a constant finding in such cases. In most instances no fungal elements were found in the destroyed lymphoid tissues. Patients with this blood dyscrasia, referred to as alymphocytosis, presented the above-mentioned toxic symptoms. All reported cases terminated fatally.[42,69,87,105,106]

5. Moniliasis in Children

Moniliasis in children and adults has usually a chronic or recurrent character. A very acute clinical course, however, has been reported occasionally in this age group, similar to that seen in infants, especially after an exogenous stimulus, such as tooth extraction.[19,107,108]

In many patients of this age group the source of infection is an endogenous one, and a long-standing history of moniliasis may be traced. At least some cases present a continuation of infantile moniliasis which may often have remained undiagnosed at an early stage.[18,32,34,95,109-112] Joulia and Le Coulant[113] characterized this type as the chronic form of older children.

A. Skin.—Skin lesions in this age group are usually deeper than in infants, and they are rarely generalized. They are frequently located about the mouth,[32,111,114] nose (Fig. 8),[32,111,114] eyelids,[111,114] elbows,[111,114] knees,[111,114] and behind the ears (Fig. 9).[113] Their appearance is usually that of somewhat weeping, more or less erythematous patches covered with macerated crusts. Superficial vesicles filled with thin pus[32,111] may be present at the borders of the plaques (Fig. 10). Some desquamation may be seen around the edges.[111,113] The morphology of these patches often resembles that of large intertriginous monilial lesions of adults.[115] Older lesions may be hyperkeratotic. In some instances whitish sharply delineated rather superficial dry scaling patches resembling ringworm or streptococcic lesions[116] are present in the face, neck, and extremities (Fig. 11),[111,116] e. g., on dorsal aspects of the hands and feet (Figs. 12, 13). Blepharitis[32,111,113] and conjunctivitis[113,114] may develop. Erosio interdigitalis blastomycetica, perlèche (Fig. 14),[117] and scalp lesions are commoner in this age group than in infants. The nails of patients with chronic onychia are usually markedly thickened and hyperkeratotic, with brown discoloration, at times with transverse ridges.[34,111,113] Paronychia is marked by periungual dusky red swelling.

Granulomatous moniliasis is characterized by chronic deep granulomatous cutaneous lesions. Hornlike structures are often superimposed over them on the forehead, cheeks, scalp or the extremities.[113,118-123] The horns may be up to 1 in. long and ¼ in. in diameter. Large ulcerating boggy granulomatous lesions with somewhat elevated margins may cover the entire extremities (Fig. 15).[124,125] The condition is usually associated with nail lesions. It generally starts as a superficial infection. Chronic oral lesions in children are usually deeper and more adherent than thrush in infants.

B. Organ Lesions.—There seems to be a greater tendency to chronic, more or less localized, pathological changes in this age group, as opposed to widespread lesions in infants. Among the lesions described in children and young adults are bronchial

and pulmonary moniliasis,[93] endocarditis,[35] osteomyelitis,[18,126] vulvovaginitis,[32,111,113] corneal ulcers,[127] panophthalmitis,[128] granuloma of the Fallopian tubes[19] and the thyroid,[19,93] abscesses of the kidney[93] and myocardium,[93] and other granulomatous and necrotic lesions. The course of the disease is usually long, and the prognosis should be guarded.

In the few cases of meningitis in which spinal fluid findings were reported,[103,129-134] the pressure was elevated, there was a moderate pleocytosis with mononuclear cells usually predominating, sugar was reduced or normal, chlorides were low, and protein was increased. Blastospores of Candida may easily be mistaken for leukocytes in smears. Meningitis in adults usually runs a more chronic course than in infants. A rapidly fatal case, however, was reported in a young adult after tooth extraction.[107]

C. Endocrine Disturbances.—Symptoms of hypoparathyroidism,[91,135,136] adrenal cortical insufficiency,[91,135] and retarded growth[32,95] and development, at times leading to severe dwarfing,[34,73,113,114] have been reported in older children. These symptoms were usually detected months or years after the onset of moniliasis. The hair, eyebrows, and eyelashes may be completely lost in the course of chronic moniliasis in this age group,[73,111,137] also without any evidence of monilial scalp lesions.[114] The remaining hair is usually thin.

6. Allergic Manifestations

Candidids (moniliids), sterile skin lesions resulting from hematogenous spread of allergenic products of Candida, may be present at any age. They are papular (Fig. 16), vesicular, scarlatiniform,[76] or eczematous[109] in character, at times very similar to the primary lesions. Asthmatic manifestations of hypersensitivity to Candida have been reported in adults.[138-140] Cure resulted from antifungal treatment.[138] I observed an infant possibly falling within this category. The patient had an extensive cutaneous, oral, and vaginal moniliasis and stools positive for Candida. He had frequent severe bouts of an expiratory type of dyspnea with substernal retractions. The symptoms disappeared after oral application of nystatin.

7. Acrodermatitis Enteropathica

There has been a controversy whether Candida plays a primary, a contributory, or any role at all in a new disease entity, acrodermatitis enteropathica.[141] C. albicans has been isolated from some but not all cases of this disease, the main symptoms of which are cutaneous eruptions, disturbances in growth and development, diarrhea, and alopecia. Most cases described under this heading strongly resemble cases usually classified as chronic widespread moniliasis.[111,114,119] When the possible etiologic role of C. albicans is considered, the reported therapeutic response of patients with this disease to diiodohydroxyquin (Diodoquin) is not altogether surprising. This quinolinol amebicide has been shown to have a certain inhibitory action in vitro on Candida albicans.[142] When given by mouth it may have been operative in eliminating the fungus from the gastrointestinal tract.

8. Some Aspects of the Pathogenicity of Candida

Some patients with moniliasis may die of terminal superinfections; others, of local organ lesions caused by the fungus, such as brain abscesses, mechanical blockage of the esophagus or renal tubules, or microabscesses in the kidney. Many lethal cases, however, have not revealed such potentially fatal organ lesions directly attributable to fungus elements[29,47] or any evidence of any other disease which might have accounted for the fatal outcome. Furthermore, systemic moniliasis has been associated with degeneration or necrosis of the liver in both humans[46,99,101] and animals,[33,143] focal myocarditis in humans[101] and animals,[143] severe degenerative changes of the renal tubules in humans,[25,96,136] and toxic changes of the adrenal glands in animals.[33] There has been no evidence of fungal elements in

such lesions. The etiological significance of Candida in the causation of alymphocytosis, the endocrine disturbances, and the toxic symptoms has remained unclear. Several workers have postulated, therefore, the existence of a toxic substance responsible for some aspects of the pathogenicity of Candida.[25,31,42,144,145] Some work has been done to demonstrate lethal properties of different cell extracts of Candida,[88,146-149] but no attempt has been made to study other effects of such extracts.

9. Endotoxin of Candida

I prepared a soluble and filterable extract by mechanical disintegration of the yeast cells of C. albicans. Mice injected intravenously with this extract developed toxic symptoms, and most of them died in less than two hours. It may be of interest that a marked loss of hair was noted in a mouse after the administration of multiple sublethal doses of the toxin.[150]

The frequent association of leukemias and other malignancies with Candida [151,152] suggests a study of the significance of its presence and of the effects of its endotoxin in such diseases. The recent demonstration of a rapid lytic action of living Candida cells on certain tumor cells in vitro and in vivo [153-154] throws new light upon this problem. Experimental work in this direction, as well as immunological, metabolic, and endocrine studies, are being conducted at present.

10. Incidence of Candida

The figures for the incidence of C. albicans in the oral cavity of various groups of healthy and sick infants of various ages, 11% to 81%, are generally higher than those, 1% to 23%, for clinically diagnosed oral thrush in infants.[5,13,36,41,155,156] C. albicans can be found in feces of apparently normal persons,[121,157,158] but almost never on normal skins or in skin disorders of other etiology.[65,157,159] Perlman did not recover any pathogenic dermatophyte or C. albicans in 68 cases of atopic dermatitis in children.[160] It has been shown, however, that nurses in an intimate contact with infants suffering from thrush are capable of harboring the fungus on their normal fingers for short periods of time.[30]

11. Epidemiology

Maternal vaginitis due to yeast-like fungi (Fig. 17); the incidence of which was found to be up to 41% in pregnant women,[155] is probably one of the commonest direct or indirect sources of infection in infants.[155,161-164] Infestation of the vagina with yeast-like fungi may at times be asymptomatic.[163] Contamination of the mouth of the newborn probably very often takes place during the passage through the birth canal.

Maternal vaginitis is obviously not always the direct source. Hands of nurses and mothers with (Fig. 18) or without clinical lesions [36]; "droplet hits" from their infected oral cavities (Fig. 14) [5]; insufficiently sterilized rubber nipples,[41] diapers, and pooled breast milk,[36] and airborne infection [4,165] are other possible sources. Large epidemics among infants in foundling hospitals in Europe decades ago [1,52] were thought to be due to long duration of hospitalization, with the inherent danger of cross infection.[166] The incidence of moniliasis in such institutions in Italy in the latter part of the last century was 10% to 60%.[88,89] The average mortality rates in six large hospitals at that time were given as 60%.[89]

The possibility of intrauterine infection [161,167] is very suggestive in view of several reported fatal cases of moniliasis in the first days of life. One newborn infant died at the age of 2 days [85]; another, when 4 days old,[168] of disseminated pulmonary infection. A fatal case of meningitis at the age of 7 days,[104] as well as one of perforation of the esophagus at the age of 3 days,[167] has been reported. A newborn infant had multiple pustular skin eruptions and onychia when one day old.[74] In cases in which contamination presumably took

place during or shortly after the passage through the birth canal the first symptoms of superficial infection are rarely seen before the eighth day of life, and systemic infections may develop weeks later. It may be of interest in this connection that at least one case of extensive endometritis due to Candida has been reported.[169]

In children and adults, Candida is frequently present as a saprophyte, probably mainly in the gastrointestinal tract, after clinical cure or without any preceding clinical manifestations of moniliasis. Such a focus may become a source of endogenous infection. An exogenous infection in this age group is also possible, since Candida is available through contact with carriers, persons with clinical disease, and contaminated objects.

It is not surprising, in view of these epidemiological findings, that there is a definite familial occurrence of thrush.[32,73,112,135] I have seen many siblings with thrush and one family in which members of three generations had symptoms of oral, cutaneous, and vaginal moniliasis.

12. Predisposing Factors

Irritation of the skin and mucous membranes by mechanical factors (urine and feces in the diaper area, tiny abrasions by a rough diaper, moisture and maceration in intertriginous areas) and bacterial infection are thought to be predisposing factors but not necessary prerequisites for the establishment of monilial infections. Patients have been found to have had a foreign body in a bronchus,[51,92] intestine,[57] or myocardium[96] for some time before they developed disseminated moniliasis. Many observers feel that premature or debiliated infants are more prone to contract thrush, but this view has not been generally accepted.[36,165] Long hospitalization may be a factor in such cases. It has been the impression of many workers that Candida infections have been increasing, especially in very young infants,[83] and that the percentage of disseminated forms of moniliasis has been higher recently as a result of antibiotic treatment, although such forms of the disease were well known and frequent decades ago. Elimination of the competing bacterial flora, or avitaminosis due to elimination of organisms synthesizing vitamins, or direct stimulation of growth of Candida by antibiotics, has been thought to be the cause. Animal experiments[170] and clinical evidence[171] seem to indicate that steroids enhance monilial infections. Isoniazid is thought to have similar effects in humans.[172] Onset of clinical moniliasis after vaccination[137,173] and immunization[93] has been reported. Cases of fatal systemic moniliasis following a tooth extraction have been reported.[19,107,108] Diabetes is often seen in children and adults with moniliasis. It is thought of by many observers as a factor predisposing to moniliasis. Moist and warm climate is said to predispose to the disease.

13. Laboratory Diagnosis

Sodium hydroxide mounts of skin scrapings and methylene-blue- or Gram-stained smears of other specimens are quick diagnostic methods, but cultures with exact mycological identification should also be employed. Details of mycelial growth on special media should be examined, including the search for chlamydospores, round thick-walled resting spores said to be formed only by the species C. albicans. Sugar fermentation tests and animal inoculation are also useful methods to differentiate species of Candida.[174] Agglutinins may be demonstrated in the sera of many patients, and positive skin reactions to extracts of C. albicans may be seen in persons who have moniliasis or who have come into contact with Candida. Both tests are of little diagnostic value.[13,174] Agglutination and skin reactions may be negative in patients with severe infections.

14. Treatment and Prevention

Aqueous solution of methylrosaniline chloride (gentian violet) (1%) has been the most popular treatment for oral thrush.

The same agent, as well as Castellani's paint, 2% iodochlorhydroxyquin (Vioform) ointment in petrolatum, 2%-5% ointment of ammoniated mercury, and potassium permanganate soaks have been used with variable results for cutaneous manifestations. Swartz's ointment containing mercurochrome and salicylic acid is effective for skin lesions. Deep cutaneous lesions and monilial granuloma may require the use of strong keratolytics. Potassium iodide by mouth, or sodium iodide or methylrosaniline chloride intravenously, has been recommended for the treatment of systemic moniliasis. An oral preparation of undecylenic acid,[95] thymol,[114] and paraben (an ester of parahydroxybenzoic acid)[12,13,20,52,175] have been claimed to have some beneficial effects in disseminated moniliasis.

A new antifungal antibiotic, nystatin (Mycostatin),[176] appears to be superior to other therapeutic agents in many forms of moniliasis. In my experience the best results in the treatment of oral thrush, often resistant to other forms of therapy, are obtained with the combination of topical applications of nystatin in suspension to oral lesions three to five times daily and oral administration of 100,000 to 200,000 units of the suspension three to five times a day.

Treatment of weeping intertriginous lesions of infants may be started with wet compresses of Burow's solution, diluted 1:20. Application of any ointment is contraindicated at this stage. After exudation has subsided, nystatin ointment may be applied two to four times daily. Improvement is usually seen within two to seven days. Alternately, topical treatment may be started with the application of shake lotions containing nystatin.[177] The course in patients with markedly erythematous skin surfaces may be shortened by topical applications of adrenal cortical steroids in lotion or ointment given prior to topical treatment with nystatin.

The response to topical treatment with nystatin is usually slower in children with deep cutaneous lesions. Good results with nystatin have been reported in granulomatous cutaneous lesions, onychia, and paronychia.[178] Crusts and excessive secretions should be removed to allow contact of the antibiotic with the lesions.

Topical treatment of moniliasis with nystatin is strikingly effective in most pediatric patients. If it is not accompanied by oral administration of the drug, however, recurrences follow frequently. Cutaneous moniliasis is usually just one symptom of infestation with Candida although it is very often the only one accessible to physical examination. On the basis of statistical and clinical evidence, it is probably wise, for practical purposes, to assume the presence of Candida in the gastrointestinal tract of any pediatric patient with cutaneous moniliasis. As was pointed out before, Candida may, under certain circumstances, become locally parasitic in this tract and produce lesions, at times accompanied by clinical symptoms such as diarrhea. In most cases of systemic dissemination it is probably the digestive tract from where the fungus starts its invasion via blood stream and lymphatics into other organs. It appears indicated, therefore, to administer an effective antifungal drug orally in conjunction with any topical treatment in children. This will often save one the disappointing experience of cutaneous recurrences and probably reduce the incidence of the fortunately rare systemic dissemination.

Vulvovaginitis in children,[69] similarly as in adults,[179] responds to oral medication; vaginal tablets (100,000 units per tablet) are also available. There is some indication that good results may be obtained with oral administration of nystatin in bronchopulmonary lesions.[69,180] Inhalation of nystatin in suspension has been claimed to have beneficial effects in pulmonary aspergillosis.[181] This method of administration might be worth a trial in bronchopulmonary moniliasis.

Doses of 100,000 to 200,000 units three to five times daily to infants and children are generally sufficient. In severe cases

1,000,000 units four or more times a day may be tried. I did not observe any side-effects in 48 children treated with nystatin. Oral treatment should be continued for several days—in chronic cases for weeks beyond clinical clearing—to prevent recurrences. Pharmacologic studies indicate that nystatin is poorly absorbed from the gastrointestinal tract.

The use of antibiotics and steroids should be avoided whenever possible. The administration of vitamin B complex has been recommended. Frequent changing of diapers in infants is essential. The skin should be kept dry.

Routine prenatal examination of vaginal secretions for fungi may detect many sources of neonatal thrush.[41,161] Treatment of pregnant women with vaginal cultures positive for Candida may prove to be an effective preventive measure in the control of neonatal thrush. Isolation of infants of mothers with monilial vaginitis and infants with thrush has been suggested in order to prevent nursery epidemics.[41,165]

Proper nursing techniques and sterilization of utensils should be observed. Nurseries should be checked for possible accumulations of dust in places difficult of access.[165]

Summary

Moniliasis may be caused by any species of Candida, but it is usually caused by C. albicans. The disease forms may range from transient benign stomatitis, comprising the majority, to generalized fatal cases. Dissemination occurs by continuity and by way of the blood stream and lymphatics.

Skin lesions in infants are more superficial and usually cover larger areas than those in older children. Moniliasis seems to be the cause of perianal dermatitis in newborn infants more frequently than is generally realized. Depigmentation occurs in Negroes. Extension by continuity may result in the formation of pseudomembranes in the esophagus, ulcers and perforation of the intestine, or pulmonary lesions.

Severe postprandial vomiting, diarrhea, toxic appearance, shock with hypothermia, and hepatosplenomegaly may suggest systemic moniliasis due to hematogenous spread. This disease form usually runs an acute, frequently fatal, course in infants. A history or symptoms of superficial involvement of the mucous membranes and skin may often help to consider the diagnosis in such cases. Abscesses in practically any part of the body may be found on autopsy. Alymphocytosis may accompany extensive moniliasis in infants and young children. Because of lack of specific macroscopic features systemic moniliasis may pass unrecognized at autopsy unless histological examination is undertaken.

Candida infections beyond infancy have usually a more chronic course and often represent a continuation of infantile moniliasis. The site of predilection for cutaneous lesions is the face and the extremities. Cutaneous granulomas, abscesses, and localized granulomatous and necrotic organ lesions, as well as meningitis, may develop in cases of long standing. Hypoparathyroidism, adrenal cortical insufficiency, retarded growth and development, and alopecia have been reported in children with chronic moniliasis. Allergic reactions to the presence of Candida include candidids, secondary sterile skin lesions, and asthmatic symptoms. Acrodermatitis enteropathica strongly resembles chronic widespread moniliasis. C. albicans is usually isolated from patients with this disease.

Preparation of a filterable toxic extract of Candida is reported.

C. albicans may be frequently found in the oral cavity and feces of infants, at times without causing clinical lesions. It is almost never present on normal skins or in skin disorders of other etiology.

Maternal monilial vaginitis, contaminated hands and objects, and airborne infection, are some of the sources of moniliasis in infants. Intrauterine infection may also occasionally occur. Infection from endogenous foci, e. g., in the gastrointestinal tract, as well as exogenous sources, is responsible

for disease beyond infancy. Familial incidence of moniliasis has been noted. Factors predisposing to thrush are listed.

Nystatin is superior to other therapeutic agents in many forms of moniliasis. Oral administration of the antibiotic in infants and children should always accompany any topical applications, since many patients have foci of infection in the gastrointestinal tract. Treatment of pregnant women with monilial vaginitis might prevent thrush in newborns. Isolation of infants with thrush is advisable.

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REFERENCES

1. Valleix, F. L. I.: Clinique des maladies des enfants nouveau-nés, Paris, J. B. Baillière, 1838, Muguet, pp. 205-462.

2. Langenbeck, B.: Auffindung von Pilzen auf der Schleimhaut der Speiseröhre einer Typhus-Leiche, Neue Notiz. aus dem Geb. Natur- u. Heilk. 12:145-147 (Nov.) 1839.

3. Fischl, R.: Die Entwickelung und der gegenwärtige Stand unserer Kenntnisse über den Soor, Zentralbl. Kinderh. 1:321-327 (Oct. 1) 1887.

4. Fischl, R.: Entwicklung und gegenwärtiger Stand unserer Kenntnisse über die Soorkrankheit, Ergebn. inn. Med. u. Kinderh. 16:107-191, 1919.

5. Epstein, B.: Studien zur Soorkrankheit, Jahrb. Kinderh. 104:129-182, 1924.

6. Buschke, A., and Joseph, A.: Soormykose (Endomykose), in Handbuch der Haut- und Geschlechtskrankheiten edited by J. Jadassohn, Vol. 11, Berlin, Springer-Verlag, 1928, pp. 893-916.

7. Plaut, H. C., and Grütz, O.: Die Hyphenpilze oder Eumyceten: II. Hauptgruppe: Die Soorpilzgruppe, in Handbuch der pathogenen Mikroorganismen, edited by W. Kolle, R. Kraus, and P. Uhlenhuth, Ed. 3, Vol. 5, Pt. 1, Jena, G. Fischer, and Berlin and Vienna, Urban und Schwarzenberg, 1928, pp. 180-204.

8. Staehelin, A.; Mu, J. W., and van Schouwen, M.: Beiträge zur Klinik und Pathogenese der Oidiomykosen, Arch. Dermat. u. Syph. 165:294-342, 1932.

9. Shelmire, B.: Thrush Infections of the Skin, Arch. Dermat. & Syph. 12:789-813 (Dec.) 1925.

10. Viklický, J.: Diseases Caused by Candida albicans, Sborn. lék. 51:153-190, 1949.

11. Winter, W. D., Jr.: Candida (Monilia) Infections in Children, Pediat. Clin. North America 2:151-161 (Feb.) 1955.

12. Mayer, J. B.: Pilzerkrankungen und moderne Pädiatrie, Kinderärztl. Praxis 23:406-417 (Sept.); 457-466 (Oct.) 1955.

13. Plenert, W.: Studie zum Verhalten von Candida in der Kinderklinik, Deutsche Gesundh. 10:1374-1380 (Oct. 20) 1955.

14. Sutton, R. L., Jr.: Diseases of the Skin, Ed. 11, St. Louis, The C. V. Mosby Company, 1956, Moniliasis, pp. 542-550.

15. Benham, R. W.: Certain Monilias Parasitic on Man: Their Identification by Morphology and by Agglutination, J. Infect. Dis. 49:183-215 (Sept.) 1931.

16. Skinner, C. E.: The Yeast-like Fungi: Candida and Brettanomyces, Bact. Rev. 11:227-274 (Dec.) 1947.

17. Duroux, Jarniou, Granetier, and Lemaire: Mycose pulmonaire mortelle provoquée par les antibiotiques, Bull. et mém. Soc. méd. hôp. Paris 70:611-619, 1954.

18. Weingart, J. S.; Wirtz, D. C., and Irving, N. W.: Monilia Osteomyelitis: Report of a Case Resulting from Thrush, Am. J. Clin. Path. 12:597-600 (Dec.) 1942.

19. Beuthe, D.: Candidasepsis, Zentralbl. allg. Path. 93:241-245 (March) 1955.

20. Wegmann, T.: Pilzerkrankungen der inneren Organe als Folge von Behandlung mit Antibiotica, unter besonderer Berücksichtigung des Respirationstraktes, Antibiotica et chemother. 1:235-275, 1954.

21. Jones, G. E. S.; Wood, J. L.; Bishop, D. W., and Donoho, R. S.: Vaginal Fungi and Their Relationship to Sperm Survival, Am. J. Obst. & Gynec. 70:1271-1276 (Dec.) 1955.

22. Mirman, J. M.: Moniliasis of the Biliary Tract: Report of Case, J. Lab. & Clin. Med. 19: 379-381 (Jan.) 1934.

23. Bontke, E.: Pilzgranulom des Hodens, Ztschr. Urol. 48:787-791, 1955.

24. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, J. A. M. A. 119: 333-336 (May 23) 1942.

25. Wikler, A.; Williams, E. G., and Wiesel, C.: Monilemia Associated with Toxic Purpura: Report of a Case, Arch. Neurol. & Psychiat. 50:661-668 (Dec.) 1943.

26. Zimmerman, L. E.: Candida and Aspergillus Endocarditis: With Comments on the Role of Antibiotics in Dissemination of Fungus Disease, Arch. Path. 50:591-605 (Nov.) 1950.

27. Köhlmeier, W.: Zur Kenntnis der Candidainfektionen, Klin. Med. 8:54-61 (Feb. 1) 1953.

28. Dubos, R. J.: Unsolved Problems in the Study and Control of Microbial Diseases, J. A. M. A. 157:1477-1479 (April 23) 1955.

29. Lederer, H., and Todd, R. McL.: Thrush in Infancy, Arch. Dis. Childhood 24:200-207 (Sept.) 1949.

30. Grasset, E., and Fleury, C.: Conceptions actuelles sur l'épidémiologie des mycoses et leur

rôle en pathologie pulmonaire: Facteurs influençant la fréquence des moniliases observées indépendamment ou consécutivement à l'emploi des antibiotiques, Praxis *42*:285-*292* (April 9) 1953.

31. Stooss, M.: Zur Aetiologie und Pathologie der Anginen, der Stomatitis aphthosa und des Soors: Untersuchungen über den Soor des Mundes, Mitth. klin. u. med. Inst. Schweiz *3*:1-30, 1895.

32. Craps, M.; Lambelin, E., and Vanbreuseghem, R.: Moniliase généralisée à Candida albicans, Arch. belges dermat. et syph. *6*:29-*52* (March) 1950.

33. Smith, L. W., and Sano, M. E.: Moniliasis with Meningeal Involvement, J. Infect. Dis. *53*: 187-196 (Sept.-Oct.) 1933.

34. Konrad, J., and Winkler, A.: Beitrag zum Problem der Moniliasis, Dermat. Wchnschr. 131: 73-82, 1955.

35. Geiger, A. J.; Wenner, H. A.; Axilrod, H. D., and Durlacher, S. H.: Mycotic Endocarditis and Meningitis, Yale J. Biol. & Med. 18:259-*268* (March) 1946.

36. Ludlam, G. B., and Henderson, J. L.: Neonatal Thrush in a Maternity Hospital, Lancet 1:64-70 (Jan. 17) 1942.

37. Wagner, E.: Zur Kenntnis des Soors des Ösophagus, Jahrb. Kinderh. 1:58-62 (Nov. 25) 1867.

38. Daireuva, M. P.: Recherches sur le champignon du muguet et son pouvoir pathogène, thesis, Nancy, A. Crépin-Leblood, 1899.

39. Ffrench, G., and Shenoi, V.: Disseminated Moniliasis with Demonstration of the Organism in the Blood, Canad. M. A. J. 71:238-241 (Sept.) 1954.

40. Heller, A.: Beitrag zur Lehre vom Soor, Deutsches Arch. klin. Med. 55:123-140, 1895.

41. Anderson, N. A.; Sage, D. N., and Spaulding, E. H.: Oral Moniliasis in Newborn Infants, Am. J. Dis. Child. 67:450-456 (June) 1944.

42. Amlie, R.: Moniliase ("Essentielle Lymphocytophthise" Glanzmann et Riniker), Ann. paediat. 179:316-320 (Nov.) 1952.

43. Reye, D.: Oesophagitis of Infants, M. J. Australia *2*:673-674 (Dec. 13) 1941.

44. Potenza, L., and Feo, M.: Contribución al estudio de las esofagitis en la infancia: Estudio clínico-patológico, Arch. venezol. puericult. y pediat. 14:224-288 (Oct.-Dec.) 1951.

45. Schmidt, M. B.: Über die Localisation des Soorpilzes in den Luftwegen und sein Eindringen in das Bindegewebe der Ösophagusschleimhaut, Beitr. path. Anat. 8:173-187, 1890.

46. de Gavaller, B.: Moniliasis en los recién nacidos, Rev. obst. y ginec. 13:203-217, 1953.

47. Ebbs, J. H.: Oesophagitis in Infancy, Arch. Dis. Childhood 13:211-224 (Sept.) 1938.

48. Langerhans, R.: Ein Fall vom Soor des Ösophagus mit eitriger Entzündung der Schleimhaut, Arch. path. Anat. 109:352-357, 1887.

49. Riemschneider, O.: Über eine tödliche Blutung infolge Gefässerosion durch Soor, Monatsschr. Kinderh. 26:71-74, 1923.

50. MacGregor, A. R., and Henderson, J. L.: Intestinal Thrush: A Report of *2* Cases in Young Infants, Arch. Dis. Childhood 18:186-187 (Dec.) 1943.

51. Hradcová, L.: Thrush Enterocolitis of Premature Infants as a Complication of Antibiotic Treatment, Pediat. listy 9:345-347 (Dec.) 1954.

52. Hottinger, A.: Klinischer Beitrag zum Vorkommen von Moniliasis im Kindesalter, Ann. paediat. 187:218-237 (Sept.) 1956.

53. Zalesky, N.: Ein Fall von Soor im Magen, Arch. path. Anat. 31:426-430, 1864.

54. Meixner, K.: Ausgebreiteter Soor des Magens, eine Verätzung vortäuschend, Deutsche Zeitschr. ges. gerichtl. Med. *25*:51-60 (June 4) 1935.

55. Engelhard, C. F.: Candida Albicans Infection in a Child, J. Pediat. *32*:404-409 (April) 1948.

56. de Forest, H. P.: Thrush: Saccharomyces Albicans, Am. J. Obst. 61:131-165 (Jan.) 1910.

57. Pavlica, F.: Peritonitis Due to Candida, Časop. lék. česk. 94:3-5 (Jan. 7) 1955.

58. Lelong, M.; Alison, F.; Le Tan Vinh; Dao Van Ty; Desmonts, G., and Cabanes, J.: Le Muguet généralisé (septicémie à Candida albicans), Ann. méd. 54:5-21, 1953.

59. Murphy, J. R., and Mallozzi, M. A.: Fungus Findings in a Diarrhea Outbreak in New-Borns, Arch. Pediat. 53:276-277 (April) 1936.

60. Beck, S. C.: Über das Erythema mycoticum infantile, Dermat. Studien 20:495-505, 1910.

61. Ibrahim, J.: Über eine Soormykose der Haut im frühen Säuglingsalter, Arch. Kinderh. 55:91-101, 1911.

62. Rasch, C.: Eczema Marginatum Hebra and Other Mycoses Resembling Eczema, Acta dermat.-venereol. 3:315-344 (Dec.) 1922.

63. Hill, L. W.: The Treatment of Eczema in Infants and Children: II. Eczematous Fungus Infections, J. Pediat. 47:363-368 (Sept.) 1955.

64. Plenert, W.: Der Hautsoor im Säuglingsalter, Kinderärztl. Praxis 23:481-485 (Nov.) 1955.

65. Bound, J. P.: Thrush Napkin Rashes, Brit. M. J. 1:782-784 (April 7) 1956.

66. Mayer, J. B.; Götz, H., and Seitz, G.: Eine Epidemie von Soormykose der Körperhaut unter dem Bilde der Erythrodermia desquamativa (Leiner), Ann. paediat. 177:213-224 (Oct.) 1951.

67. Mármarosi, G.; Oláh, D., and Tuza, K.: Kann die generalisierte Form des Erythema mycoticum infantile mit der Leinerschen Krankheit

in Verbindung gebracht werden? Dermat. Wchnschr. 129:313-321, 1954.

68. Le Coulant, P., and Marchand, A.: A Propos d'une observation d'érythème fessier des nourrissons due à Candida albicans, J. méd. Bordeaux 125:208-210 (May) 1948.

69. Dobias, B.: Cutaneous Moniliasis in Pediatrics: Diagnosis and Treatment with Nystatin, in Therapy of Fungus Diseases: An International Symposium, edited by T. H. Sternberg and V. D. Newcomer, Boston, Little, Brown & Company, 1955, pp. 205-210.

70. Pardo-Castello, V.: Achromia Parasitaria: Its True Nature and Etiology, Arch. Dermat. & Syph. 25:785-789 (May) 1932.

71. Pardo-Castello, V., and Martinez Dominguez, M.: Achromia Parasitaria, Arch. Dermat. & Syph. 9:82-95 (Jan.) 1924.

72. Schamberg, F.: Meeting of the Philadelphia Pediatric Society March 9, 1915, Arch. Pediat. 32:617-620 (Aug.) 1915.

73. Schlutz, F. W.: Systemic Thrush in Childhood, J. A. M. A. 105: 650-653 (Aug. 31) 1935.

74. Klopstock, E.: Oidiomykosis pustulosa miliaris disseminata corporis et unguium, Arch. Dermat. u. Syph. 149:477-485 (Nov. 20) 1925.

75. Park, D. R.; Desmond, M. M., and Fahlberg, W. J.: Monilia Onychia: Report of a Case in a 51-Day-Old Premature Infant, J. Pediat. 44:313-316 (March) 1954.

76. Holzel, A.: Skin Thrush in Early Infancy, Arch. Dis. Childhood 28:412-415 (Oct.) 1953.

77. Ballowitz, L., and Schäfer, H.: Das Auftreten von Mykosen bei antibiotischer Behandlung im Kindesalter: Ein Beitrag zur Diagnostik und Therapie, Monatsschr. Kinderh. 102:336-340 (July) 1954.

78. Swift, S.: Diaper Dermatitis, Pediat. Clin. North America 3:759-769 (Aug.) 1956.

79. Lorenz, E.: Über einen Fall von Soorkrankheit mit ungewöhnlichen Lokalisationen, Ztschr. Kinderh. 47:164-165, 1929.

80. Heubner, O.: Über einen Fall von Soorallgemeininfektion, Deutsche med. Wchnschr. 29:581-583 (Aug. 13); 604-606 (Aug. 20) 1903.

81. Maciucescou-Manoël, M., and Pincou, J.: Sur Un Cas de muguet du larynx (croup à Oidium albicans, tubage, trachéotomie, guérison), Arch. méd. enfants 28:231-235 (April) 1925.

82. Langer, E.: Über den Soor des Kehlkopfes, Arch. Laryng. u. Rhin. 34:159-163, 1921.

83. Gerloczy, F.; Schmidt, K., and Scholz, M.: Beiträge zur Frage der Moniliasis im Säuglingsalter, Ann. paediat. 187:119-133 (July-Aug.) 1956.

84. Skogrand, A.: Broncho-Pulmonal Moniliasis, Nord. med. 51:276-278 (Feb. 18) 1954.

85. Schürmann, R.: Über Soormykosen nach antibiotischer Behandlung, Ärztl. Wchnschr. 8:719-721 (July 24) 1953.

86. Vince, S., and Csillag, A.: Beiträge zur Klinik der Candidiase (Moniliensepsis) des Säuglingsalters, Ann. paediat. 187:134-151 (July-Aug.) 1956.

87. Glanzmann, E., and Riniker, P.: Essentielle Lymphocytophthise: Ein neues Krankheitsbild aus der Säuglingspathologie, Ann. paediat. 175:1-32 (July-Aug.) 1950.

88. Concetti, L.: Biologie et pathogénie du muguet, Arch. méd. enfants 3:449-479; 517-541; 590-605, 1900.

89. Guidi, G.: Über Soor, seine Mykologie und Metastasenbildung, Wien. med. Bl. 19:371-372 (June 11); 390-391 (June 18); 406-407 (June 25); 422-423 (July 2); 436-438 (July 9); 453-454 (July 16); 468-470 (July 23); 485-487 (July 30); 501-502 (Aug. 6); 516-517 (Aug. 13); 533-534 (Aug. 20) 1896.

90. Mucci, A.: Oidiomicosi della pelle, Gior. ital. dermat. e sif. 66:644-648, 1925.

91. Craig, J. M.; Schiff, L. H., and Boone, J. E.: Chronic Moniliasis Associated with Addison's Disease, A. M. A. Am. J. Dis. Child. 89:669-684 (June) 1955.

92. Cardelle, G.: Moniliasis en la infancia: Observaciones acerca del diagnóstico y tratamiento por el Micostatin (Nystatina), Rev. méd. cubana 66:653-671 (Sept.) 1955.

93. Gausewitz, P. L.; Jones, F. S., and Worley, G., Jr.: Fatal Generalized Moniliasis: Report of a Case, Am. J. Clin. Path. 21:41-49 (Jan.) 1951.

94. Venturi, T.: Contributo alla cosi detta blastomicosi cutanea: Un caso di dermatomicosi da Endomices Albicans Wuillemin, con grave setticemia, Dermosifilografo 13:450-466 (July) 1938.

95. MacDonald, G., and Cohen, T. M.: Moniliasis (Systemic?); Chronic Hepatomegaly; Pigmentation, A. M. A. Arch. Dermat. & Syph. 65: 373-375 (March) 1952.

96. Clinical Pathological Conference, Children's Medical Center, Boston, J. Pediat. 49:330-341 (Sept.) 1956.

97. Debré, R.; Mozziconacci, P.; Drouhet, E.; Drouhet, V.; Hoppeler, A.; Grumbach, R., and Habib, R.: Les Infections à Candida chez le nourrisson, Ann. paediat. 184:129-164 (March) 1955.

98. Schmorl, G.: Ein Fall von Soormetastase in der Niere, Zentralbl. Bakt. 7:329-335, 1890.

99. Vanbreuseghem, R.; Balsacq, J., and Bertrand: Moniliase généralisée par Candida alb. chez un enfant indigène au Congo belge après un traitement par les antibiotiques, Ann. Soc. belge méd. trop. 32:513-519 (Oct. 31) 1952.

100. Lamy, M.; Aussannaire, M.; Jammet, M. L., and Caramanian, M.: Un Cas de mycose sous-cutanée à Candida albicans, Arch. franç. pédiat. 10:71-73, 1953.

101. Broz, O., and Kopriva, K.: A Case of Moniliasis in an Infant with Rare Affection of the Heart and Pleura, Pediat. listy 8:211-215 (Aug.) 1953.

102. Kunstadter, R. H.; MacLean, H., and Greengard, J.: Mycotic Endocarditis Due to Candida albicans, J. A. M. A. 149:829-832 (June 28) 1952.

103. Carron, R., and Chavanis, P.: Méningite à "Candida albicans" après antibiothérapie prolongée locale et générale, Pédiatrie 9:387-390, 1954.

104. Campos, J. de O.: Méningo-encéphalite mycosique chez un enfant âgé de 7 jours, Rev. clin. Inst. maternal 3:39-44, 1951.

105. Donohue, W. L.: Alymphocytosis, Pediatrics 11:129-139 (Feb.) 1953.

106. Betke: (Discussion), Verhandl. deutsch. Gesellsch. inn. Med. 58:715, 1952.

107. Morris, A. A.; Kalz, G. G., and Lotspeich, E. S.: Ependymitis and Meningitis Due to Candida (Monilia) Albicans: Report of a Fatal Case of Meningitis, with Comment on Its Clinical, Bacteriologic and Pathologic Aspects, Arch. Neurol. & Psychiat. 54:361-366 (Nov.-Dec.) 1945.

108. Bartels, H. A., and Buchbinder, M.: Yeast-like Microorganisms Isolated from Root Canals, Oral Surg. 7:98-102 (Jan.) 1954.

109. Hopkins, J. G.: Moniliasis and Moniliids, Arch. Dermat. & Syph. 25:599-614 (April) 1932.

110. Pillsbury, D. M., and Gibson, T. E.: Moniliasis Cutis, Arch. Dermat. & Syph. 57:423-424 (March) 1949.

111. MacLeod, J. M. H.: Skin-Diseases Due to Monilia and Other Yeast-like Fungi, Brit. J. Dermat. 42:549-561 (Dec.) 1930.

112. Miller, J. L.: Moniliasis, Arch. Dermat. & Syph. 54:484-485 (Oct.) 1946.

113. Joulia, P., and Le Coulant, P.: Les Épidermomycoses généralisées de la seconde enfance par champignons levuriformes, Ann. dermat. et syph. 10:545-570 (July 7) 1939.

114. Baird, K. H.: Unusual Syndrome Associated with Candida Albicans Infection, Pediatrics 4:730-734 (Dec.) 1949.

115. Hopkins, J. G.: Ringworm and Moniliasis, Pennsylvania M. J. 41:455-472 (March) 1938.

116. Belisario, J. C.: Cutaneous Moniliasis, M. J. Australia 2:538-542 (Oct. 27) 1934.

117. Finnerud, C. W.: Perlèche: A Clinical and Etiologic Study of 100 Cases, Arch. Dermat. & Syph. 20:454-488 (Sept.) 1929.

118. Hauser, F. V., and Rothman, S.: Monilial Granuloma: Report of a Case and Review of the Literature, Arch. Dermat. & Syph. 61:297-310 (Feb.) 1950.

119. Čajkovac, S., and Puretić, S.: Candidiasis Granulomatosa, Radovi Medicinsk. fak. u Zagrebu 3:245-260, 1953.

120. Langer and Ruppert: Generalisierte Oidiomykose (Candida albicans), Arch. Dermat. u. Syph. 200:588-589, 1955.

121. Robinson, H. M., Jr.: Moniliasis Complicating Antibiotic Therapy: Clinical and Laboratory Studies, A. M. A. Arch. Dermat. & Syph. 70:640-652 (Nov.) 1954.

122. Pels, I. R.; Dresel, I., and Salinger, R.: An Unusual Eruption Due to an Organism of the Monilia Group: A Preliminary Report, Arch. Dermat. & Syph. 14:280-293 (Sept.) 1926.

123. Downing, J. G., and Hazard, J. B.: Cutaneous Moniliasis Associated with Oral Thrush: An Unusual Case, Arch. Dermat. & Syph. 31:636-643 (May) 1935.

124. Watrin, J.; Beurey, J., and Mougeolle: Les Moniliases cutanées, Rev. méd. Nancy 79:240-251 (April 1-15) 1954.

125. Ferguson, E. H., and Rothman, S.: Fungus Infections of the Skin, Pediat. Clin. North America 3:555-595 Candidiasis (Moniliasis, Oidiomycosis, Thrush), (Aug.) 1956, pp. 573-578.

126. Connor, C. L.: Monilia from Osteomyelitis, J. Infect. Dis. 43:108-116 (Aug.) 1928.

127. Sykes, E. M.: Fungus Infections of the Cornea: Case Report of Keratomycosis Due to Monilia, Texas J. Med. 42:330-332 (Sept.) 1946.

128. Baker, R. D.: Histopathology of the Mycoses, Washington, D. C., American Registry of Pathology, 1945.

129. Halpert, B., and Wilkins, H.: Mycotic Meningitis Due to Candida, J. A. M. A. 130:932-934 (April 6) 1946.

130. Zimmerman, S. L.; Frutchey, L., and Gibbes, J. H.: Meningitis Due to Candida (Monilia) Albicans with Recovery, J. A. M. A. 135:145-147 (Sept. 20) 1947.

131. Miale, J. B.: Candida Albicans Infection Confused with Tuberculosis, Arch. Path. 35:427-437 (March) 1943.

132. Craig, W. McK., and Gates, E. M.: Metastatic Mycotic Abscesses of the Brain, Arch. Neurol. & Psychiat. 62:314-321 (Sept.) 1949.

133. Attal, C.: Mycoses cérébro-méningées, Ann. méd. 51:445-494, 1950.

134. Emdin, W., and Finlayson, M. H.: Moniliasis of the Central Nervous System in a Child with Recovery, South African M. J. 28:868-871 (Oct. 9) 1954.

135. Whitaker, J.; Landing, B. H.; Esselborn, V. M., and Williams, R. R.: The Syndrome of Familial Juvenile Hypoadrenocorticism, Hypoparathyroidism and Superficial Moniliasis, J. Clin. Endocrinol. 16:1374-1387 (Oct.) 1956.

136. Case Records of the Massachusetts General Hospital: Weekly Clinicopathological Exercises;

Case 40361, New England J. Med. 251:442-448 (Sept. 9) 1954.

137. Bensoussan-Chetboul, L.: Contribution à l'étude du traitement des cas graves d'infection à Candida albicans par la Fungicidine, thesis, Paris, 1955.

138. Keeney, E. L.: Candida Asthma, Ann. Int. Med. 34:223-226 (Jan.) 1951.

139. Sclafer, J.: Un Cas d'asthme à Candida (Monilia) albicans, Semaine hôp. Paris 30:1555-1557 (April 14) 1954.

140. Dutton, L. O.: Mold Fungi in the Etiology of Respiratory Allergic Diseases: X. Intrinsic Fungus Factors in Relation to Asthma, Ann. Allergy 7:585-591 (Sept.-Oct.) 1949.

141. Sulzberger, M. B., and Baer, R. L.: Some Recent Advances in Dermatologic Mycology: Tinea Pedis; Trichophyton Rubrum Infections; Tinea Capitis; Moniliasis, in The Year Book of Dermatology and Syphilology (1954-1955 Year Book Series), Chicago, The Year Book Publishers, Inc., 1955, pp. 7-33.

142. Beck, O., and Lacy, H.: The Effect of Certain Antibiotics, Antimalarial Drugs and Amebicides on Candida Albicans, Texas Rep. Biol. & Med. 9:395-405 (Fall) 1951.

143. Adriano, S. M., and Schwarz, J.: Experimental Moniliasis in Mice, Am. J. Path. 31: 859-873 (Sept.-Oct.) 1955.

144. Roger: Les Endotoxines microbiennes, Compt. rend. mém. Soc. biol. 67:161-162, 1909.

145. Peruchena, J. G. H., and Pedace, E. A.: Moniliasis: Estudio histológico de las alteraciones celulares y de las lesiones observadas en los animales de experimentación, Semana méd. 36: 1075-1085 (Oct. 10) 1929.

146. Buss, A.: Ein Beitrag zur toxischen Wirkung vom Oidium albicans, abstracted, Zentralbl. Bakt. 62:368-369 (Aug. 4) 1914.

147. Thomas, E.: Über einige Wirkungen der Soorbestandteile, Jahrb. Kinderh. 96:95-100, 1921.

148. Krauspe, C.: Untersuchungen zur Biologie des Soorpilzes und zur Pathogenese der Soorkrankheit, Krankheitsforschung 4:1-28; 139-163, 1927.

149. Salvin, S. B.: Endotoxin in Pathogenic Fungi, J. Immunol. 69:89-99 (July) 1952.

150. Dobias, B.: Unpublished observations.

151. Diller, J. C., and Fisher, M.: Isolation of Fungi from Transplanted, Chemically Induced and Spontaneous Tumors: I. General Considerations, Cancer Res. 10:595-603 (Oct.) 1950.

152. Bernard, J.; Mathé, G., and Drouhet, E.: Les Infections à Candida au cours des hémopathies décompensées et leur traitement par la nystatine, Sang 26:490-495, 1955.

153. Castelli, V., and Gaggini, V.: Antibiotiques pour cellules carcinomateuses? Schweiz. med. Wchnschr. 78:424-428 (May 8) 1948.

154. Diller, J. C.; Mankowski, Z. T., and Harris, L. T.: Lytic Action of Candida and Saccharomyces Sp. on Sarcoma 37 and Ehrlich Ascites Tumors, Cancer Res. 14:848-852 (Dec.) 1954.

155. Woodruff, P. W., and Hesseltine, H. C.: Relationship of Oral Thrush to Vaginal Mycosis and the Incidence of Each, Am. J. Obst. & Gynec. 36:467-471 (Sept.) 1938.

156. Haler, D. H.: Bronchomoniliasis, Brit. M. J. 1:1052-1053 (June 4) 1932.

157. Benham, R. W., and Hopkins, A. McH.: Yeast-like Fungi Found on the Skin and in the Intestines of Normal Subjects: A Survey of 100 Persons, Arch. Dermat. & Syph. 28:532-534 (Oct.) 1933.

158. Schnoor, T. G.: The Occurrence of Monilia in Normal Stools, Am. J. Trop. Med. 19:163-169 (March) 1939.

159. Marwin, R. M.: Relative Incidence of Candida Albicans on the Skins of Persons With and Without Skin Diseases, J. Invest. Dermat. 12:229-241 (April) 1949.

160. Perlman, H. H.: Fungus Studies in Atopic Dermatitis: Failure to Demonstrate Pathogenic Fungi in the Lesions, J. Pediat. 34:458-459 (April) 1949.

161. Cron, R. S.: Thrush Vaginitis, Tr. Am. A. Obstetricians 42:225-229, 1929.

162. Plass, E. D.; Borts, I. H., and Hesseltine, H. C.: Yeast Vaginitis: Its Possible Etiological Relationship to Oral Thrush in the New-Born, J. Iowa M. Soc. 20:121-123 (March) 1930.

163. Plass, E. D.; Hesseltine, H. C., and Borts, I. H.: Monilia Vulvovaginitis, Am. J. Obst. & Gynec. 21:320-334 (March) 1931.

164. Hesseltine, H. C.; Borts, I. C., and Plass, E. D.: Pathogenicity of the Monilia (Castellani), Vaginitis and Oral Thrush, Am. J. Obst. & Gynec. 27:112-116 (Jan.) 1934.

165. Faber, H. K., and Clark, E. B.: Prevention and Treatment of Thrush (Oidial Stomatitis), Am. J. Dis. Child. 34:408-417 (Sept.) 1927.

166. Blasi, P.: Della riforma materiale dei brefotrofi, quale unico mezzo profilattico contra il mughetto endemico, Arch. ital. pediat. 9:1-12 (Jan.) 1891.

167. Veron: Mémoire sur le muguet, Arch. gén. méd. 8:466, 1825.

168. Birch-Hirschfeld: Soorknötchen in pneumonischen Herden der Lungen eines viertägigen Kindes, Jahresb. Gesellsch. Natur. u. Heilk. Dresden 6:31, 1875.

169. Langerhans, R.: Mycosis uteri, Berlin. klin. Wchnschr. 31:611-612 (June 25) 1894.

170. Mankowski, Z. T., and Littleton, B. J.: Action of Cortisone and ACTH on Experimental Fungus Infections, Antibiotics & Chemother. 4:353-358 (March) 1954.

171. Levy, E. S., and Cohen, D. B.: Systemic Moniliasis and Aspergillosis Complicating Corticotropin Therapy, A. M. A. Arch. Int. Med. 95: 118-122 (Jan.) 1955.

172. Pesle, G. D., and Labéguerie, M.: Deux Cas de moniliase digestive au cours de traitement par l'isoniazide, Rev. tuberc. 17:881-882, 1953.

173. Keller, W.: Soorangina nach Impfung, Klin. Wchnschr. 15:683-684 (May 9) 1936.

174. Conant, N. F.; Smith, D. T.; Baker, R. D.; Callaway, J. L., and Martin, D. S.: Manual of Clinical Mycology, Ed. 2, Philadelphia, W. B. Saunders Company, 1954.

175. McVay, L. V., Jr., and Sprunt, D. H.: A Study of Moniliasis in Aureomycin Therapy, Proc. Soc. Exper. Biol. & Med. 78:759-761 (Dec.) 1951.

176. Hazen, E. L., and Brown, R.: Two Antifungal Agents Produced by a Soil Actinomycete, Science 112:423 (Oct. 13) 1950.

177. Osbourn, R. A.: Nystatin Topical Therapy of Moniliasis: Preliminary Report, A. M. A. Arch. Dermat. 72:371 (Oct.) 1955.

178. Grupper, M. C.: Traitement de quelques dermatoses à levures (Moniliase à type de pyodermite végétante, intertrigo, onyxis, et perionyxis) par un nouvel antifungique: Mycostatin ou nystatin, Bull. Soc. franç. dermat. et syph. 61:495-497 (Nov.-Dec.) 1954.

179. Sarewitz, A. B.: Treatment of Genitourinary Moniliasis with Orally Administered Nystatin, Ann. Int. Med. 42:1187-1189 (June) 1955.

180. Beckmann, A. J., and Navarro, J. E.: Pneumonia Complicating Oral Thrush Treated with Mycostatin, a New Antifungal Antibiotic, J. Pediat. 46:587-591 (May) 1955.

181. Riddell, R. W.: Fungous Diseases in Britain, Brit. M. J. 2:783-786 (Oct. 6) 1956.

Gastric Perforation in the Newborn Infant

Postoperative Wound Evisceration and Survival

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Gastric perforation in the newborn infant is a rare entity. Less than one-half of the recorded cases have had surgical exploration, and approximately only one in three of those undergoing surgery has survived. Usually exploration is done too late or the correct diagnosis is made at necropsy. Perforation of the stomach (and duodenum) must be considered in the differential diagnosis of the acute abdomen in the neonatal period to ensure earlier closure of the perforation and a higher survival rate. This is the 12th report of a survival of gastric perforation in a newborn infant. The patient is of additional interest because the infant survived despite a postoperative wound evisceration.

Report of Case

A 6 lb. 12 oz. white boy was born at Garfield Memorial Hospital, Washington, D. C., on March 23, 1956. The mother was a 29-year-old primagravida, and the labor was uncomplicated. The baby appeared normal at birth and was given routine neonatal care. On March 25, 1956, the infant began regurgitating feedings and spitting up large amounts of mucus. Lavage of the stomach with a soft rubber catheter was performed on the third day, and a large quantity of bile-tinged mucus was obtained. On the fourth morning he again vomited. The temperature was normal. That morning he was seen by his pediatrician (M. J. F.), who noted that the patient seemed to be in pain and that his abdomen appeared distended. The patient was then transferred to Children's Hospital, Washington, D. C., on March 27, 1956, at 10:30 a.m.

Physical examination on admission revealed a 6 lb. 7 oz. white boy who did not appear acutely ill. His color was good, and he cried when disturbed. The important findings were confined to the abdomen. The abdomen was moderately distended, although soft to palpation. There was only a suggestion of muscle guarding on the right. Liver dullness was obliterated, and bowel sounds were hypoactive. Upright films revealed a large amount of air beneath the diaphragm. Roentgenograms of the chest were unremarkable. A diagnosis of a visceral perforation was made. Preoperatively, the patient's blood was typed and cross matched for transfusion and a clysis of 2.5% dextrose in Hartmann-Ringer's solution was started. This was followed by a 5% dextrose in water for injection U. S. P. through a cut-down incision in an ankle vein. In addition, the baby was given a penicillin and streptomycin preparation (Dicrysticin), intramuscularly, and he was placed in an oxygen tent.

At 4:20 p.m., with use of ether-oxygen anesthesia, the abdomen was opened through a right rectus paramedian incision. There was approximately 50 cc. of amber-colored fluid in the abdominal cavity. Plastic exudate was present in the subhepatic space. A perforation measuring 3 mm. in diameter was found on the anterior wall of the pyloric end of the stomach. There was no evidence of surrounding induration. The perforation was closed with interrupted nonabsorbable surgical (silk) sutures tied over a piece of free omentum. The peritoneal cavity was thoroughly irrigated with isotonic saline solution. The peritoneum was closed with a continuous 000 chromic absorbable surgical (gut) suture, reinforced with interrupted 0000 silk. The anterior rectus sheath was approximated with interrupted chromic 000 gut sutures. The skin was closed with interrupted 0000 silk sutures. No drains were used. Culture of the peritoneal fluid showed no growth. Pathologic report of the plastic exudate was necrotic tissue with many polymorphonuclear leukocytes.

Postoperatively, the patient was placed in an incubator (Isolette) with oxygen and Wangensteen suction was started. He was given blood, fluids, and vitamins B and K and ascorbic acid, intravenously. Because of the precarious condition of the infant and the serious nature of his illness, a combination of broad-spectrum antibiotics was started as a prophylactic measure. Dicrysticin was given twice daily in doses of 0.5 cc. intramuscularly. The next day chloramphenicol (Chloromycetin), 50 mg., was administered intramuscularly

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twice daily. These drugs were continued for a total of 10 and 9 days, respectively.

On March 28, 1956, a phlebitis of the right leg developed, necessitating removal of the polyethylene catheter. Another cut-down infusion was started in the left ankle vein, and on March 30 this was also discontinued because of phlebitis.

Oral fluids were started on March 30, 1956. However, the baby vomited and became cyanotic, and the abdomen became distended. Roentgenograms of the chest and abdomen were unremarkable at that time. Oral feedings were temporarily discontinued. At 4:00 a.m., April 1, 1956, wound dehiscence occurred immediately after a feeding. The resident reported that 4 to 5 in. of bowel had appeared on the abdominal wall. Saline compresses and sterile towels were placed over the abdomen. The operating room was alerted, and the patient's blood was cross matched for transfusion. When the surgeon (D. J. A.) arrived, at 4:20 a.m., it was noted that approximately 18 in. of bowel was protruding through a 1½ in. opening in the superior portion of the wound. A 5 in. segment of the bowel and mesentery was black, as a result of compression of the blood supply. The wound was immediately enlarged, at the bedside, to relieve compression on the mesenteric vessels, and the baby was then taken to the operating room. With use of ether-oxygen anesthesia, the abdomen was prepared with benzalkonium (Zephiran) solution. The wound was further enlarged, and all loose sutures were removed. Warm saline compresses were applied to the abdominal contents for approximately 10 minutes. The questionable segment of bowel finally responded to pinching and appeared viable. The distended stomach was decompressed by nasogastric suction. Rapid exploration of the abdomen revealed the area of perforation to be well healed. There was no evidence of peritonitis. The necrotic exudate in the subhepatic space had disappeared. A specimen for culture was not taken. The intestines were replaced, and the peritoneal cavity was thoroughly irrigated with isotonic saline solution, followed by instillation of 1,000,000 units of penicillin. A soft rubber tissue drain was placed in the subhepatic space and was brought out through a stab wound on the right. The wound was closed with through-and-through interrupted stainless steel wire sutures No. 30.

The baby's immediate postoperative condition was poor. He was transfused with 70 cc. of blood through a cut-down incision in the left brachial vein. In addition to previous measures, he was given adrenal cortex extract. By that evening, his general condition had improved. Peristaltic sounds were audible, and flatus was passed. On April 3, 1956, the catheter in the left brachial vein slipped out. Thereafter, further fluid therapy was administered by the subcutaneous route. On April 4, 1956, he was fed a high-protein formula in small amounts by gavage. Oral feedings were instituted the next day. The rubber tissue drain was removed on April 7, 1956. By April 10, 1956, he was taking 2½ oz. of modified cow's milk (Bremil) every three hours. He was discharged from the hospital on April 13, 1956, weighing 6 lb. 4 oz. The sutures were removed in the office on April 17, 1956, and examination revealed his condition to be satisfactory. Six months later the baby weighed 15 lb. and he was in excellent health.

Incidence

Peptic ulceration of the stomach and duodenum is rarely encountered in infancy and childhood. Proctor [12] found only 2 children in a study of 8260 necropsies of ulcer patients at the Mayo Clinic. Guthrie,[4] in 1942, reported 9 cases of peptic ulceration in 6059 necropsies at the Glasgow Hospital for Sick Children. Six of the nine cases were under 3 months of age. Hutchins,[6] in 1944, reviewed the literature and found 243 cases of peptic ulceration in infancy and childhood; 77 had perforation. Bird, Limper, and Mayer,[1] in 1941, noted that there were 119 operated-on cases in the literature, and they found the mortality rate in the newborn to be 80%.

The first recorded gastric perforation in a newborn infant was by Siebold,[13] in 1825. It was not until 1929 that surgical repair on such a patient was attempted, by Stern and associates.[14] The patient did not survive. Légar et al.,[9] in 1950, were the first to record a successful repair of a gastric perforation in the neonatal period. In 1955, Vargas and associates [15] stated that there were 55 recorded cases of perforation of the stomach; 22 had surgery, and 9 survived. They added 11 cases from the Babies Hospital of the Columbia-Presbyterian Medical Center. Two, of the eight that were operated on, survived.

Etiology

In the newborn infant perforation of the duodenum is usually a result of peptic ulceration, whereas perforation of the stomach can be due to other causes. An increased gastric acidity in the first few days

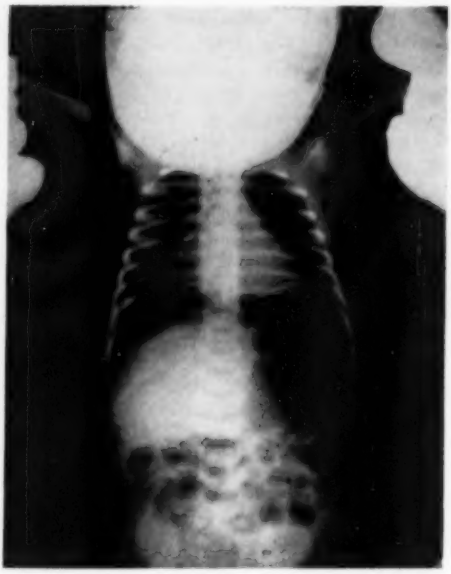
of life has been found by Miller.[10] Local vascular injury or trauma and the increased acidity may terminate in digestion of the stomach wall. We feel that this combination of circumstances was of etiologic import in our patient. The traumatism associated with the use of a rubber nasogastric tube cannot be excluded as a contributing factor, despite the fact that the gastric symptoms antedated the use of the tube.

Gastric perforations associated with the use of nasogastric tubes have been reported by Kellogg,[8] Potter,[11] and Vargas et al.[15] When a soft rubber catheter is used, such an accident is unlikely. The incidence is higher with the use of polyethylene tubes. Perforation is more apt to occur when a congenital defect in the gastric musculature is present. These congenital defects were first described by Herbut,[5] in 1943. In such cases, the tears are large and are located in the fundus or cardia. In the presence of a large perforation, distal obstruction in the intestinal tract should not be overlooked as an initiating factor. Obstruction, when present, is most commonly found in the duodenum or pylorus.

Other etiologic factors are prematurity, intracranial hemorrhage, and sepsis. Over 50% of the cases reported were in premature infants. Intracranial hemorrhage is a frequent finding and leads to injury of the vasomotor centers of the brain, as described by Cushing.[2] Gastric perforation may be associated with septicemia. Necrosis of the stomach is often found in association with generalized sepsis.

Diagnosis

Awareness of the possibility of duodenal or gastric perforation in the newborn infant will lead to earlier diagnosis and survival of a greater number of these patients. The early symptoms are minimal. Vomiting or regurgitation of feeding in the first few days of life warrants investigation. The stools may become less frequent and contain blood. Sudden abdominal distention is the first definite warning sign. With increasing distention, cyanosis occurs because of interference with respiration. Late symptoms are those associated with dehydration and shock. Examination will reveal the presence of abdominal distention. The abdomen is soft to palpation, with questionable spasm, usually on the right. Liver dullness is obliterated. The upright roentgenogram of the abdomen is the most important diagnostic aid and will demonstrate pneumoperitoneum (Fig.). It is important to stress that newborn babies requiring a roentgenographic examination of the abdomen should have an upright film taken routinely.



Upright film, demonstrating a large collection of free air beneath the diaphragm.

Treatment

Perforated gastric or duodenal ulcer in the newborn infant is a surgical emergency, and medical or expectant treatment is not indicated. An ample right rectus incision is made. The abdomen is quickly explored in order to rule out congenital or obstructive lesions, which have occurred in a significant number of cases. We prefer to close the perforation with through-and-through sutures of a nonabsorbable material, tied over a piece of free omentum. The edges of the

ulcer are not excised. A search for additional perforations is made. The abdomen is thoroughly irrigated with isotonic saline solution, and a suitable antibiotic is instilled into the abdominal cavity. Some surgeons close the wound without drainage. We feel that it is wiser to place a drain in the subhepatic space because of reported reperforations or leaks. Early reperforation, thus, would be discovered quickly. Closure of the abdominal incision is accomplished according to the individual preference of the surgeon. It would appear that nonabsorbable sutures would lend greater support to the abdominal wound since the wounds in infants are subject to fairly continuous strain because of crying and distention.

Postoperative Care

The postoperative treatment is important. The patient is placed in an incubator where the temperature and humidity are constant and oxygen can be administered. Wangensteen suction is maintained for several days. Others prefer intermittent passage of stomach catheters with aspiration of the stomach contents. Intravenous fluids, consisting of blood, plasma, and electrolyte solutions, to which are added vitamins B and K and ascorbic acid, are given through a cut-down incision in an ankle vein. Hypernatremia and overloading the circulation with fluids must be avoided. As soon as possible, return to oral feedings is indicated. First dextrose in water is tried in small amounts. Later the infant is fed a dilute formula, which is gradually increased in amount and strength. Until adequate oral fluid intake is obtained, supplementary fluids can be given by the subcutaneous or intravenous route. Antibiotics are prescribed for the first four or five days, or longer if necessary.

Wound Disruption and Evisceration

Wound evisceration with survival in the newborn period is undoubtedly rare. Gross [3] found only 75 cases of evisceration in a series of 8319 major intra-abdominal operations in children. It is noteworthy that 64 of these patients were under 2 years of age. The incidence of evisceration in his entire group was 0.9%, and the mortality rate was 45%.

Wound disruption has been blamed on many factors, not the least of which is abnormal metabolism of the healing process. Therefore, the best treatment is still preventative and all abnormal body states should be promptly corrected. When hypoproteinemia exists, insufficient amino acids are present for normal collagen formation. Edema of tissues associated with chemical imbalance slows the healing process. Vitamins are also important in good wound healing; with deficiency of ascorbic acid there is depression in collagen formation and atrophy of connective tissue. Lack of vitamin B complex results in lowered resistance and atony of the intestines. Vitamin A is a requisite for normal epithelialization. In the newborn, hypoprothrombinemia due to vitamin K deficiency predisposes to bleeding into the wound and hematoma formation.

In infancy and childhood an important causative factor in wound disruption is the increased intra-abdominal pressure caused by crying, straining, gastric dilatation, or ileus. Active measures should be taken to avoid abdominal distention, but when this is present it is treated by gastric or intestinal intubation. Oxygen therapy is a worthwhile adjunct.

Of the many types of abdominal incisions, the upper, vertical rectus wound is the most prone to disrupt. The preponderance of transverse fibers in the posterior sheath of this area may cause any type of suture to pull through, particularly when the posterior sheath is thin or when an inhalation anesthetic is poorly administered. Emphasis must be placed on meticulous surgical techniques, sharp dissection, and careful hemostasis in the prevention of wound disruption. The needles and sutures used should be the smallest compatible with adequate closure. Triple-throw square knots are preferable. Strangulation of tissue by tying sutures too tightly should be avoided. Since continuous

chromic gut suture is most often used for peritoneal closure, reinforcement of this layer with interrupted sutures is advantageous. Nonabsorbable sutures are preferable in the fascial layer. Drains should be placed through stab wounds—not in the wound itself.

Disruptions occur, despite the type of suture material used. Jenkins[7] has suggested measures to preserve the strength of gut sutures. Gut should never be handled with a clamp, stretched before it is made pliable, or immersed in hot water. Loss of strength may be due to imperfections in the gut itself. Rapid digestion of this material may be due to the presence of hematomas, infection, serum collections, or allergic reactions to chromic gut.

In our patient, the evisceration occurred through a 1½ in. opening in the superior portion of the wound. It was felt that crying and distention of the abdomen caused the sutures to pull through the posterior rectus sheath. There was no evidence of gross infection or disintegration of sutures in the remainder of the incision. The nutritional status of the patient was adequate, since he had received appropriate fluids, blood, and vitamins.

With the possibility of wound disruption, suggested by the sudden appearance of serous drainage, or when actual disruption without evisceration has occurred, the wound should be treated expectantly by the application of a firm adhesive dressing. This may prevent evisceration but will usually result in a postoperative hernia, which can be repaired at a later date. Evisceration, however, is an acute surgical emergency and demands immediate replacement of the viscera and wound closure. To combat shock, fluids, blood, and general supportive measures are necessary. Warm sterile towels are placed over the wound, and the patient is immediately taken to the operating room. The abdominal wall is prepared with aqueous benzalkonium chloride solution (1:1000) or other suitable antiseptics, and the wound is then draped. All loose sutures are removed from the wound. The viscera are replaced, and the abdominal cavity is thoroughly irrigated with warm isotonic saline solution. Antibiotics are injected into the peritoneal cavity. Closure of the wound is then carried out with through-and-through nonabsorbable sutures, preferably steel wire. Tamponade with gauze and adhesive strapping should be reserved for critical patients who could not possibly withstand a surgical procedure.

Summary

A case of perforation of the stomach in a newborn infant, complicated by later wound evisceration, with survival is presented. This patient is the 12th recorded survival of surgically treated perforation of the stomach in the newborn infant. The rarity of evisceration in the newborn infant with survival is also emphasized. A discussion of gastric perforation and evisceration in the newborn infant is presented.

Farragut Medical Building (6).

REFERENCES

1. Bird, C. E.; Limper, M. A., and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children, Ann. Surg. 114:526, 1941.

2. Cushing, H.: Peptic Ulcers and Interbrain (Balfour Lecture), Surg. Gynec. & Obst. 55:1, 1932.

3. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953, pp. 53-54.

4. Guthrie, K. J.: Peptic Ulcer in Infancy and Childhood with Review of Literature, Arch. Dis. Childhood 17:82, 1942.

5. Herbut, P. A.: Congenital Defect in the Musculature of the Stomach with Rupture in a Newborn Infant, Arch. Path. 36:91, 1943.

6. Hutchins, L. R.: Peptic Ulcer in Children: Case Report of Perforation, Northwest Med. 43:40, 1944.

7. Jenkins, H. P.: A Clinical Study of Catgut in Relation to Abdominal Wound Disruption, Surg. Gynec. & Obst. 64:648, 1937.

8. Kellogg, H. G.; Abelson, S. M., and Cornwall, F. A.: Perforation of the Stomach in Newborn Infant, J. Pediat. 39:357, 1951.

9. Léger, J. L.; Ricard, P. M.; Leonard, C., and Piette, J.: Ulcère gastrique perforé chez un nouveau-né avec survie, Union méd. Canada 79: 1277, 1950.

10. Miller, R. A.: Observations on Gastric Acidity During the First Month of Life, Arch. Dis. Childhood 16:22, 1941.

11. Potter, E. L.: Pathology of the Fetus and Newborn, Chicago, The Year Book Publishers, Inc., 1952, pp. 295-296.

12. Proctor, O. S.: Chronic Peptic Ulcer in Children, Surg. Gynec. & Obst. 41:63, 1925.

13. Siebold, cited by Thiele, P.: Über Geschwürsbildungen des Gastro-duodenal-tractus im Kindesalter, Ergebn. inn. Med. u. Kinderh. 16:302, 1919.

14. Stern, M. A.; Perkins, E. L., and Nessa, N. J.: Perforated Gastric Ulcer in a 2-Day-Old Infant, Journal-Lancet 49:492, 1929.

15. Vargas, L. L.; Levin, S., and Santulli, T. V.: Rupture of the Stomach in the Newborn Infant, Surg. Gynec. & Obst. 101:417, 1955.

Nursery School

Notes for the Physician

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The physician is consulted today not only when a child is ill but equally as often when parents have questions or problems regarding their child's physical, mental, or social development.[1] One of the frequent questions asked is "Doctor, shall I send my child to nursery school?"

This paper will discuss what the physician should know in order to help parents evaluate whether nursery school is the answer to their child's and their own needs. To be able to give such help, the physician should know and appraise (*a*) the parents' motivations for considering nursery school at this time; (*b*) the young child's basic needs for healthy growth and development and how these needs can be met; (*c*) the function of the nursery school in relation to meeting the needs of the young child and of his parents; (*d*) the child's readiness for the nursery school experience.

It is our hope that this analysis of the various factors which motivates parents to send their children to nursery school and of what the nursery school can offer to supplement the needs of the young child may serve as a basis of reference to the physician in his consultations with parents.

Parents' Motivation for Considering Nursery Schools

Parents are often motivated to consider nursery school by their own needs as well as their child's needs for healthy growth and development. The physician who recognizes and accepts this can acknowledge these needs with the parents and in this manner alleviate their feelings of guilt or inadequacy in seeking out the aid of the nursery school. He may find that parents frequently look to the nursery school for help in meeting several needs, such as the following[2-5]: (*a*) their child's need for play and companionship with children around his own age; for help in social adjustment—in learning to get along with others, in learning to share, cooperate, and gain independence, and for help in emotional adjustment—in learning to cope with the feelings of frustration which are imposed by restrictions in daily living and (*b*) their own need for help in understanding and management of their child; for free time for other duties and activities; for giving their child optimal opportunities for physical, mental, and social well-being, and for working outside the home and leaving their child under supervised care.

It is in clarifying with parents their motivations for considering nursery school that both physician and parents will gain a more clear awareness of the problems and needs that parents hope will be met by the nursery school. In some cases the physician and parents become aware that nursery school is not the answer. For example, the physician may find parents looking to the nursery school for help with their 4-year-old child's unintelligible speech and hyperactive behavior. In this case the physician may recommend further medical studies, including hearing evaluation and psychometric testing, before considering nursery school as a possible solution to this child's speech and behavior problem.

In another case, that of parents who complain that their child frequently sets fires

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in closets, the physician may find parents who not only disagree continuously and are inconsistent in the management of their child but who also appear to be using their child as a pawn to work out their personal and marital problems. In this case, a referral to a psychiatrist, a mental hygiene or child guidance clinic, or a family service agency—depending on the resources of the family and the resources available in the community—would be more beneficial.

On the other hand, the physician may see families where a supplement like the nursery school could be of great help. For example, he may encounter parents who receive more satisfactions and feelings of worth from social activities or a career than from child care and homemaking. The physician who recognizes and understands this can accept these parents, rather than feel and behave critically toward them, and can help them to provide opportunities, like nursery school, which would be beneficial to their child's development.

The physician may also find parents who present problems such as this: "Johnny has become so mean and demanding lately. I feel that if he had playmates it would help him to learn to get along with others and he would be much happier." The physician's evaluation of this situation may reveal a 4-year-old Johnny who does not have playmates and a mother so busy with housework and with the care of Johnny's brothers and sisters that she has little time or energy to provide for, or supervise, his play activities. The family may live in a small, crowded apartment or home on a busy street, with no safe outdoor play space and blocks away from a park or playground. This would add to the irritation and frustration of both mother and child; for a mother finds it hard to be loving and patient with a child underfoot almost constantly. The nursery school can offer the parent and child some freedom and time apart, with resultant increased enjoyment of each other when together.

The physician, however, may find many parents who can provide playmates, materials, and play space but who feel more adequate and secure in the understanding and management of their children under the educational guidance of the nursery school. In such circumstances he can appreciate how the changes in the economic and social structure of our society and the many changing concepts of health have contributed to feelings of insecurity in the parental role.[6] Apartment living, with little space for indoor or outdoor play; the increasing number of working mothers who need a place to leave their young child, and the rearing of children without the aid of grandparents or other relatives to share in home and child care responsibilities have called for some provision such as a nursery school to help meet the needs of the young child and his parents. In addition, widespread public communication via television, radio, innumerable journals, and advertisements—each acclaiming a different product or way toward physical or mental health—has added confusion and much question as to the best way to raise children.

A new emphasis on early child care and training has resulted[6] from the recognition by medical science of the importance of the early years of childhood for physical, mental, and social development as well as their influence on delinquency and mental illness. Increasing awareness of how early attitudes and experiences shape the adult mind and determine his set of values and feelings about himself have also made the physician and the parent feel more keenly the imperativeness of intelligent guidance of the young child. However, it is important that the physician help the parent to consider the nursery school only as a supplement to the home in the promotion of the health and welfare of the child and in the education of the parents.

The Young Child's Basic Needs for Healthy Growth and Development

A nursery school is defined as a school whose program is suited to the needs of the preschool child. The physician can in-

form parents as to what these needs are, how they are met in the home, and how they can be supplemented in the nursery school. For healthy growth and development the preschool child needs not only well-planned, adequate meals at regular times, adequate sleep and rest, and medical and dental care but also the security of a family in which he receives the love and affection of his parents and where parents define and maintain safe limits for his behavior and provide time to play, playmates, and a place to play indoors and out in the fresh air, along with guidance when needed.[7]

The physician can also help the parents to understand that the child's growth is not merely a biological process but also a psychological process, in that the child's need for love and dependence in order to feel secure, his need for accomplishment and achievement in order to build self-confidence and growth toward independence, and his need for help in understanding his feelings in order to control his behavior are dependent on a loving, guiding relationship with his parents.[8] The foundations for the child's feelings of adequacy and confidence arise from the manner in which his basic needs are met—through the child's experiences with feeding, toileting, play, and the satisfaction he gets in exploring the world. The attitudes and the feelings of his parents, therefore, are the most important factors, because the child is almost totally dependent on them for the satisfaction of these basic needs. Parents can also help to build their child's feelings of security and adequacy by giving understanding and acceptance to the feelings that motivate his behavior rather than blaming or shaming him and by helping him to learn acceptable expression for these feelings. Of necessity, the child depends on parents to define and maintain safe limits for his behavior in those situations in which he cannot judge the consequences of his actions, which include matters of safety, health, the rights of others, and protection against the violence of his own feelings—as in anger—and their expression in destructive ways.

The Function of the Nursery School

The nursery school can supplement the home in meeting these needs through play with other children; suitable buildings, materials, and equipment, and professional guidance during the school experience. The physician's knowledge of what constitutes a good nursery school can enable him to assist parents in deciding whether a nursery school or some other resource, like a child guidance clinic or an informal play group, will best meet their own need and that of the child.

A good nursery school provides a supervised program by trained teachers who promote learning through the use of well-planned equipment and materials. The function of the nursery school is to promote the child's health, independence, and self-confidence and feeling of security with adults and other children; to help him to understand himself and express his feelings constructively; to help him to understand and enjoy others, and to enrich his enjoyment of the arts and sciences at his level of readiness.[2-5]

The physician can help the parents to make their own evaluation of the available nursery school by letting them know that the kind of experience a child has in nursery school will depend on the number of children in the group, the length of the school day, the training and experience of the staff, the suitability of equipment and materials, and the physical set-up of the school. Since large groups and long hours create strains and reduce the contribution which the school can make to the individual child, a group of less than 20 children is recommended, at least one teacher to every 8 to 10 children (two adults in every group, no matter how small), and a two- or three-hour school session. Young children will profit from group experience only if they can receive individual care when they need it and are not too fatigued. The child's level of readiness will also determine what he will gain from the nursery school experience.

The criteria that parents can use in evaluating and choosing a nursery school can be divided into four categories: the philosophy and objectives of the nursery school program as they relate to the philosophy of child training at home, the training of the teachers and an adequate number to staff the school, the physical set-up of the school, and the program of parent education. These are mutually interdependent and necessary in carrying out the function of the nursery school.

In the area of philosophy and objectives of child training, it is most important that there be harmony and cooperation between the home and school, so that the child will not be confused or subjected to two different sets of standards and expectations. Problems may arise when a child enters nursery school and finds that the pattern of authority is different from the one at home. Following any change in authority, children may go through a period of being impudent and resistant to limits. At this time the child needs considerable understanding and guidance from parents and teachers so that he can learn to express his feelings, assert himself, and accept the necessary limits in a way that is constructive and socially acceptable.

The staff is the second important criterion to use in evaluating a nursery school. The questions parents should clarify are these: Is the staff trained and accredited in nursery school education? Is there an adequate number to provide guidance and opportunity for physical, mental, social, and emotional development? Is the teacher's guidance directed toward building the child's feelings of adequacy and security? How does the staff foster the child's development?

In promoting social and emotional development, the trained nursery school teacher helps the child to recognize and express his feelings in a constructive way, to understand the feelings and behavior of other children, and to develop acceptable social approaches and responses. She also helps the child to learn cooperative behavior, to understand personal and property rights, and to use language to secure social cooperation. She encourages the child's self-reliance and growth toward independence by suggesting investigation, trial of different methods, i. e., habits of constructive thinking in the solution of his problems.

Throughout the child's play in the nursery school, his sense of security is fostered by the teacher's interest and the reasonable certainty of what he can expect in the way of rules and support. The teacher provides not only support and opportunity to grow toward independence but also sets limits to behavior in order to protect the child from outside dangers and his own strong impulses until he can develop control.

In promoting the child's physical development, the trained teacher provides guidance for the safe use of equipment; precautions in regard to contagious diseases; midmorning snacks (in some schools, lunch), to aid nutrition and to encourage desirable eating habits and attitudes; encouragement of matter-of-fact attitudes and ultimate independence in toileting; scheduled rest periods, and the balancing of physically active with more restful play.

The trained nursery school teacher also provides materials and guidance to encourage the child's mental development, such as books and story hour, nature study, dramatic play, art, and music, in a way that enables the child to participate, enjoy, and obtain feelings of achievement and satisfaction.

The third criterion for evaluating a nursery school is the building, grounds, and equipment. Parents should clarify the following questions: Are the buildings, grounds, and equipment safe, well-lighted, and sanitary? Is there enough space for the group, both indoors and outdoors, for quiet and active play? What is the relation of indoor and outdoor play areas and of toileting facilities and play areas in regard to safety and ease of supervision? Are there suitable materials and equipment, and are they so arranged as to ensure an environ-

ment which encourages the child's physical, social, and emotional growth? Along with adequate staff, the nursery school building, grounds, and equipment are important factors in determining not only the health and safety conditions but also the learning possibilities within the school.

Parents can evaluate the program of parent education that a nursery school offers by clarifying the following points. Is the program focused toward helping parents feel more adequate and successful by offering opportunities for understanding the developmental needs and behavior of young children? What opportunities does the nursery school offer to parents for observation, discussion, individual conference, group meetings, group projects, and lectures?

Through observation in the nursery school, parents can gain reassurance and perspective concerning their child's development in relation to other children. This is especially true if parent observations are guided by lists of questions and suggestions and followed by discussion, so that questions may be answered and erroneous impressions corrected.

Individual conferences, informal or planned, can also help parents to feel more adequate. The first conference should take place before the child is entered in the school. At this time the teacher can learn the parents' motivations for sending their children to nursery school and what they hope the school can provide. In individual conferences parents may discuss their problems or concerns, which may vary from single ones due to lack of information to complex problems which are symptoms of disturbed parent-child relationships. The nursery school teacher who is a sympathetic listener, who does not give false reassurance, who helps the parent to see the child's behavior in the light of its meaning, and who directs parents who need professional help to child guidance or family counseling facilities serves well as a parent educator.

Study groups in which questions can be raised and explored through discussions also play an important part in parent-education programs. The success of a study group depends upon the homogeneity of education of the group, the training of the leader, the discussion of topics of common interest, and the convenience of time of meeting. Parents gain reassurance as well as confidence to face and work out their own solutions through the experience of participating in the discussion of problems they all share. Group projects in which parents participate may also increase parents' feelings of confidence and satisfaction in their parental roles. Talks regarding such topics of common interest as discipline, nutrition, or stages of development may be helpful only if the speaker presents the material in a way that will not increase parents' anxieties and create further problems.[4]

Parent education is one of the most important objectives of the cooperative nursery school. The greatest single factor in parent education in the cooperative nursery school is the actual participation by parents in the school activities. Under the guidance of a trained head-teacher, a mother learns to understand the developmental needs of her child and his age group while working one day a week as an assistant teacher. Fathers also become active participants through group projects, such as repair and maintenance of building and equipment and evening discussion meetings. Parent participation also helps to bring the nursery school within the reach of groups of parents who are interested in promoting their child's development but who cannot afford the fees of a private nursery school.

The Child's Readiness for Nursery School

When a child is ready for nursery school depends on the child, the school, and the available alternatives. In determining readiness, the physician can help the parents take into consideration not only the health of the child but also his physical, mental, and social maturity. Where exposure to communicable disease and upper respiratory infection would be damaging (as in rheumatic heart

disease or fibrocystic disease), the physician may recommend a program that would be more suitable to the child's physical needs.

The physician should orient the parents as to the stages of physical and emotional maturation, so that they may know what to expect and can estimate their child's readiness for nursery school. At about 2 years of age a child will show increasing signs of his sense of individuality, but not to the extent that he will be able to share his possessions or communicate his needs, owing to a limited vocabulary, or to leave the support of his mother. He will have a great sense of "mine" but very little of "yours." Also, during this period he may need more individual help with eating and toileting than a nursery school can provide. Going to nursery school, then, makes demands that are beyond the emotional capacities of most 2-year-olds. At 2½ years the child may seem very contrary. He will begin to have a taste of his own power and of the attention and commotion he can cause when he asserts himself boldly with a "no!" He has little control of his own impulses and wants what he wants right away. He will need much help from his parents in learning to tolerate the frustrations caused by denial or postponement before he is ready or mature enough for the nursery school group experience. By 3 years some children may be sufficiently mature and secure to take turns, cooperate with other children, and understand and conform to the social adjustments necessary for group participation. They are ready and eager for creative play, alongside as well as with other children. It is important for a parent to understand that as a child becomes less dependent on his mother, both physically and emotionally, he becomes more interested in testing and acquiring physical strength and prowess. He then gains much gratification from the creative activity and games which a nursery school can provide. However, in addition to this stage of readiness, the child requires preparation and gradual introduction to the nursery school, so that he can adjust at his own rate.

The physician may want to call the parents' attention to another factor in terms of the child's maturity, i. e., the available nursery school. Is it a morning, whole-day, or cooperative school? Except for working mothers who may have no other resource or alternative, a whole-day school for the preschool child is not recommended. Large groups and long hours create strains and fatigue and reduce the contribution which the school can make to the child. Parents who understand the function of the nursery school and the factors that enable the nursery school to carry out its function will be able to choose one that will best meet their child's needs.

While the physician can indicate what a nursery school can offer to supplement the home in meeting the needs of the young child, it is important that he help parents recognize that the home has very important contributions to make which are beyond the scope of the nursery school. No school can give the child the family sense of security in which he has his own unique place, where he gets his sense of worth and belonging, and where he learns by identification with his parents' behavior his future role in society. Although the nursery school teacher will show affection to all the children, it cannot replace that which is experienced in the family and is so necessary for emotional growth and maturity.

Basically, all children need individual acceptance and respect from adults, affection and approval, consistent friendly guidance, and opportunity to learn through first-hand experience. In this way they will develop respect for themselves and others, self-control, and freedom to learn at their own individual rates. In these areas the nursery school can supplement the home, with some promise for social, mental, and physical health. However, the nursery school can never be a substitute for the home or take over the parents' job; it can only aid the parents to a better understanding and guidance of their children.

Summary

In order to function in the role of consultant when parents question him on whether or not they should send their child to nursery school, the physician should (*a*) help the parents to become aware of their motivations for considering nursery school, so they may be better able to evaluate whether nursery school or another facility can meet their child's and their needs; (*b*) help parents to understand the child's basic emotional and physical needs at various ages, and how they can be met, in order that they may evaluate whether or not their child requires a supplement like the nursery school; (*c*) inform parents of what constitutes a good nursery school, so they may be able to appraise the available nursery schools; (*d*) help parents to evaluate the child's emotional and physical readiness for nursery school.

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REFERENCES

1. Spock, B.: Teaching the Broader Aspects of Pediatrics, Pediatrics 5:21-23 (Jan.) 1950.

2. Landreth, C.: Education of the Young Child, New York, John Wiley & Sons, Inc., 1942.

3. Updegraff, R., and others: Practice in Pre-School Education, New York, McGraw-Hill Book Company, 1938.

4. Read, K. H.: The Nursery School: A Human Relationship Laboratory, Philadelphia, W. B. Saunders Company, 1952.

5. Kellogg, R.: Nursery School Guide: Theory and Practice for Teachers and Parents, Boston, Houghton Mifflin Company, 1949.

6. Health Supervision of Young Children, New York, American Public Health Association, 1955.

7. Your Child From One to Six, Children's Bureau Publication No. 30, Washington, D. C., U. S. Department of Health, Education, and Welfare.

8. Allen, F. H.: Psychotherapy with Children, New York, W. W. Norton & Company, Inc., 1942.

A Longitudinal Study of the Babinski and Plantar Grasp Reflexes in Infancy

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Numerous writers have attested to the fact that the Babinski toe sign may be present in normal children up to 3 years of age. Most of the observations have been made on series of children of different ages rather than on repeated tests on the same children as they passed through successive ages. To the thus-observed incidence of Babinski reactions in normal infants have become appended a number of surmises:

1. It is generally inferred that in any individual infant the Babinski sign may be present at birth and may then remain demonstrable for an unpredictable time until it permanently disappears, before the age of 2 or 3 years.

2. It is usually agreed that this early present sign is due to lack, or irregularity, of myelinization of nerve fibers and that the disappearance of the sign marks the maturation of myelinization.

3. It has been repeatedly stated that the occurrence of a spontaneous Babinski sign in the young infant is pathological.

Routine observation of infants in the newborn nursery and in subsequent periodic check-ups raised some doubts about the validity of these secondary assumptions. Accordingly, standardized examinations were recorded on a series of infants each time they were seen in the first one or two years of life. The majority were examined at monthly intervals from birth to 6 months of age and thereafter were checked every two or three months. At each visit a complete physical examination was done, and notations were made regarding the response to Babinski, Chaddock, Gordon, and Oppenheim maneuvers. Any evidence of spontaneous Babinski sign was also recorded.

In the first part of the study attempts to elicit the Babinski sign were conducted as follows: The finger nail was lightly drawn near the lateral edge of the plantar surface of the foot from near the heel towards the fifth toe, and then mesially to stop over the distal end of the first metatarsal. It was very perplexing to find that virtually no newborn infants showed a Babinski sign. A considerable number showed an initial extension of the great toe, but as the testing finger traversed the ball of the foot the toes usually instantaneously (but sometimes haltingly) went into tight plantar flexion. After a number of months of observation it was finally realized that the Babinski response was being obscured by an even stronger plantar grasp reflex. A chance encounter with Parmelee,[1] in his excellent book on the newborn infant, reenforced my certainty of the error of my method and the logic of the conclusion drawn from it. Wrote Parmelee, "Care must be taken in stroking the lateral plantar surface not to touch the ball of the foot, since that will invariably cause flexion of the toes (a grasp reflex)." Babinski's original paper[2] (and it might be mentioned it consisted of just 28 lines, including summary) simply stated "stroke the plantar surface" of the foot. Thereafter the observations on the Babinski reaction were made after stroking only the lateral plantar surface of the foot. A column for "plantar

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grasp reflex" was added to the protocols, and a separate test was made and recorded for this reflex.

Materials

The results to be presented are drawn from 857 examinations on 103 infants under the age of 2 years. Seven hundred thirty-one of the observations were on infants under one year of age. Because of the early error in testing technique, not all protocols were suitable for consideration on all points studied. Thus, while the total group could not be used for some observations on the grasp or elicited Babinski sign, figures on the spontaneously occurring Babinski sign could validly be recorded from all protocols. Because of the vicissitudes of private practice, not all infants were followed for the same length of time. Thus, there are more protocols with observations at 3 than at 9 or 18 months of age. Consequently, no attempt can be made to translate these results into meaningful percentages; the rather general conclusions drawn from these observations are not, however, thereby compromised.

Results

Spontaneous Babinski Sign.—Because it is frequently stated that a spontaneously occurring Babinski sign is indicative of neurologic pathology, special attention was paid to such occurrence. Figure 1 shows the number of times a spontaneous sign was observed at different ages; it is obviously primarily a phenomenon of the newborn period, and, as such, possible effects of maternal anesthetic, subclinical cerebral edema, and temporary anoxia cannot be completely discounted. Although the Babinski sign evoked by testing is part of a mass flexion reflex (which has many trigger points), the spontaneously occurring sign was seen with equal frequency when the legs were extended. It was bilateral one-half of the times that it was noted. Among 76 babies seen originally as newborns, spontaneous signs were seen in 14 at two different monthly examinations and in 7 on three different occasions. With the exception of a 2 lb. premature infant, who had spontaneous Babinski signs shortly after birth and who died 16 hours later, all of these infants seemed normal at the time and have since developed normally.

It appears that a spontaneous Babinski sign is a common finding in the newborn period, occurs relatively frequently up to 3 months of age but only occasionally thereafter, and carries with it no threat of clinically recognizable pathology, in an otherwise normal infant.

The Babinski Sign in Infancy.—A discussion of the history, fascinating phylogenetic significance, and neurologic importance of,

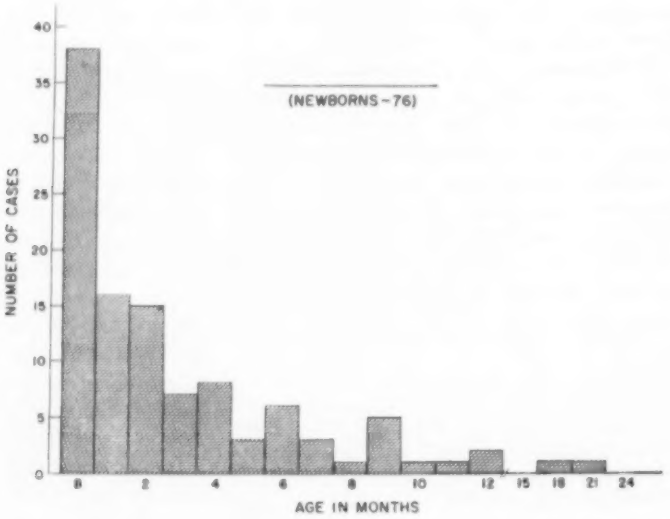


Fig. 1.—Graph showing the number of times a spontaneous Babinski sign was observed at various ages.

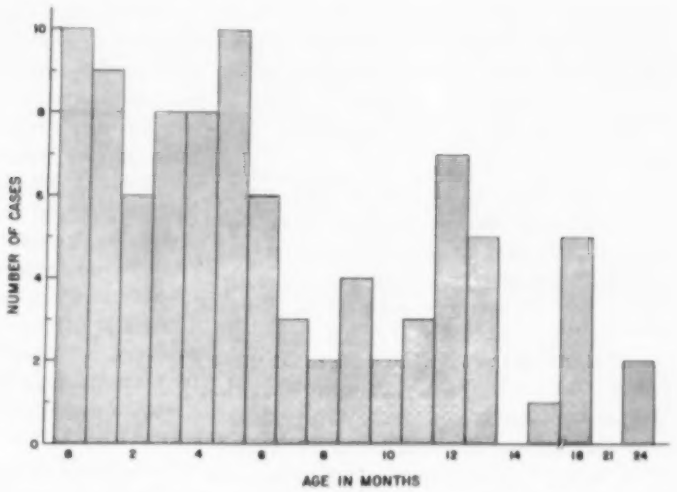


Fig. 2.—Graph showing the total number of times and ages at which a Babinski sign was demonstrated.

and ultimate attempts to supplant, the Babinski sign with inconsequential modifications is not within the province of this paper. The delightful, scholarly, and pleasantly impassioned review of Wartenberg [4] presents all these facts. Most texts [5-8] emphasize the common occurrence of the Babinski sign in normal infants. De Anglis,[9] in studying 88 newborn infants, stressed the variations noted in the response of the same baby at different moments and emphasized the tendency to mass reaction on strong stimulation. With this in mind, three to five tests of each reflex were made at every examination. As shown in Figure 2, the Babinski sign was frequently present during the first 6 months of life and much less commonly observed thereafter. In the 91 instances in which the sign was elicited, it was bilateral 35 times. Of more interest, in 47 babies a Babinski sign was readily demonstrated a month or more after the sign had failed to be obtained. Fourteen babies showed Babinski signs on two different occasions

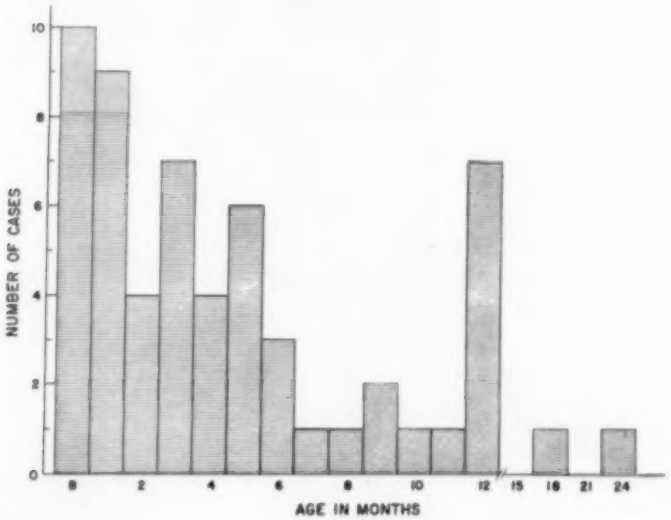


Fig. 3.—Graph showing the number of times Babinski sign was demonstrated for the first time at the various ages.

each preceded by examinations which failed to demonstrate a sign; in all instances examinations were separated by a month or more.

Figure 3 shows the number of times a Babinski sign was first elicited at each age period.

If the absence of the sign indicates myelinization, and the presence of it in the infant, incomplete or absent myelinization of the tracts involved, it is impossible to explain the foregoing observations. Without further explanation (of the sign as found in normal infants) Ford [5] states that "most observers agree the movement of extension [sic, of the great toe] is not identical with the true Babinski reflex." Perhaps if, instead of discarding the Babinski sign as meaningless in young infants, we study it more intently when we find pathologic conditions in that group of patients, we will be able to differentiate a pathologic reflex from the apparently positive sign observed in normal infants. However, it is somewhat disarming to know that within two years of his original publication Babinski [3] (who had seen no young children) predicted that the sign would be demonstrable in normal young infants.

Related Toe Signs.—Although the Chaddock,[10] Gordon,[11] and Oppenheim [12] signs were tested for at each visit, no significant information was obtained. The Chaddock sign was present in approximately as many newborns as was the Babinski, but, for the most part, different babies displayed the two signs. On only 11 examinations was there at any time a correlation between any one of these three signs and the Babinski. One cannot but concur with Wartenberg, who in warm but studied deference says, ". . . it has been my experience that the good old method of Babinski, carefully applied, is by far the best and most reliable."

The Plantar Grasp Reflex.—Psychologists and physiologists have long been interested in the palmar grasp reflex of infants, yet Halverson [13] in a 75-page report of studies of such responses fails to mention the existence of a plantar grasp reflex. McGraw,[14] in her excellent monograph on "The Neuromuscular Maturation of the Human Infant," fails to mention the plantar grasp reflex, but she does state, pertinent to our present subject, that "some striking behavior patterns of the newborn appear to be only residuals of phylogenetic functions which have lost their usefulness to the human species." The modern infant, even as his fairly recent human antecedents, does not need to hang on with his hands and feet from the moment of birth. Burr,[15] while studying the "plantar reflex" (of Babinski), mentions foot grasp, in two neonates, and describes it "as if trying to grasp with all toes at once."

If a finger or pencil is drawn across, or laid firmly and flatly on, the ball of the foot at the base of the toes, the young infant will tightly flex the toes, and slightly adduct and flex the great toe, in an apparent attempt to grasp the stimulating object (Fig. 4). This reaction is usually concise and rapid; occasionally it is slow and deliberate, and rarely it is delayed one to three seconds and then performed. A roughly similar, but less precise, reaction, without participation of the

Fig. 4.—Plantar grasp reflex in a 10-week-old infant.

great toe, is not infrequently seen in children over 2 years of age. This latter response is apparently more related to tickling than an attempt to grasp.

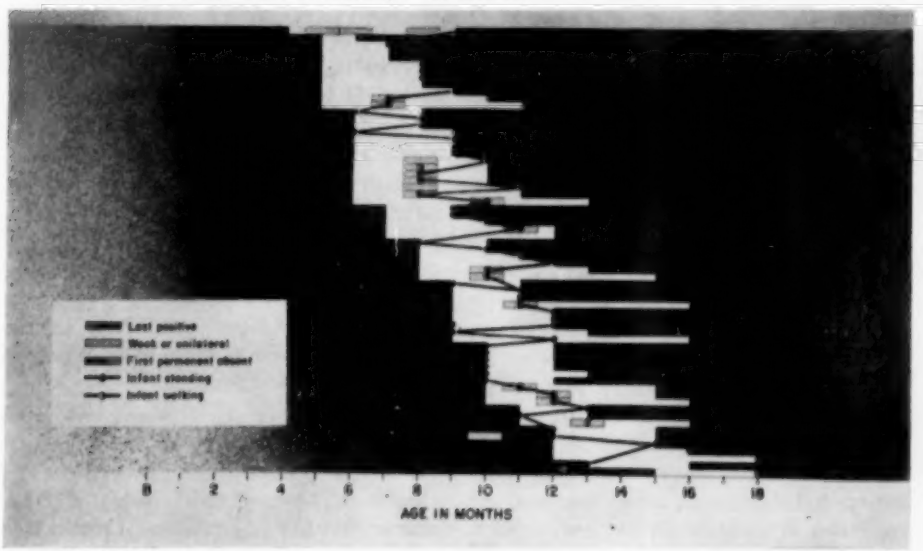
Sixty-six babies were first examined within a few days of birth. Of these, seven showed no plantar grasp reflex when first checked. Two were babies in extremis. The remaining five babies, between 1 and 3 days of age, looked and acted normal. Maternal anesthesia and sedation may have played a role in suppressing the plantar grasp reflex, though such affects were not otherwise clinically apparent. Four additional, apparently normal, newborn infants, all in the first day of life, had either weak, halting, or unilateral plantar grasp reflexes. With these exceptions, totalling 11 babies, all newborn infants had well-developed plantar grasp reflexes when first examined. Buchanan[16] states, "in the first few hours of life, however the deep reflexes and the plantar responses may be absent." It is at least of passing interest that Richter,[17] in observing the palmar grasp reflex in five newborn Rhesus monkeys, found it weak at birth and increasing in strength during the first 17 days of life.

After the newborn period the plantar grasp reflex remained positive with remarkable consistency and vigor, until its permanent disappearance. In the interval between the beginning of standing with support and actual walking some infants showed a transitional stage, with only a unilateral, a halting, or a very weak plantar grasp reflex. Figure 5 charts the age at which the plantar grasp reflex was last positive and also the age at which testing first failed to demonstrate the reflex.

Comment

Virtually all of the literature on the incidence of the Babinski sign in infants is confounded by the failure to recognize the plantar grasp reflex as an independent neurologic sign. The earliest writers, apparently reluctant to attach Babinski's name to his sign, called it the plantar reflex and then recorded their results as either extension of the great toe (with or without fanning), plantar flexion of all the toes, or some intermediary, inconsistent, or absent reaction. Morse[18] must have done his testing with unconscious avoidance of the grasp-stimu-

Fig. 5.—Graph showing the observed relationship between the disappearance of the plantar grasp reflex and the advent of standing in 63 infants.



lating area, for he was able to record "no response" in 35% of 254 infants tested for a Babinski sign. He concluded that "there was no constant plantar reflex" (Babinski sign). Feldman,[19] in studying 500 children (1 day to 8 years of age) perpetuated the error of considering the Babinski sign and plantar flexion of the toes as antipodal reactions of one reflex.

In the present study, when proper testing techniques were finally used, it was readily possible to distinguish the Babinski sign and the plantar grasp reflexes as independent neurologic entities. Of the two, the plantar grasp reflex remained regularly demonstrable until its final and permanent disappearance. The appearance and disappearance of the Babinski sign could only be observed, not forecast. The last decisively positive plantar grasp reflex was most often seen in the 6- to 10-month age period. Halverson [13] noted that the palmar grasp reflex usually disappeared by 6 months of age; Ford [5] states, "the grasping reflex [palmar] . . . disappears between the second and the fourth month." In light of the infant's more rapid voluntary control of the upper extremities, it might have been predicted that a phylogenetically important reflex of the lower extremity would disappear at a later date.

The first consistent failure to elicit a plantar grasp reflex shows a much wider chronologic scattering. This was probably largely due to the longer and more irregular intervals between examinations after the infants reached 6 months of age. However, in the instances where there was an opportunity to observe it, the change in grasp reflex from present to absent was usually definite within a one- to two-month interval.

Because it appeared that the loss of the palmar grasp reflex might logically be related to increasing voluntary use of the hands and arms in the 2- to 6-month age period, it seemed pertinent to see if there was any correlation between standing (voluntary and functional use of the feet and legs) and loss of the plantar grasp reflex. In the latter part of the study, the visit at which the parents answered in the affirmative the question "Does he pull himself up to standing in his crib or pen?" was recorded. Except for rare instances in which this momentous event was associated with a remembered date, it was simply recorded as an accomplished fact at the time of the visit in question. Obviously, in some instances the child had been standing for several months before the recorded age of accomplishment. In Figure 5, when a vertical, and perforce zig-zag, line is dropped through these "standing points" it is seen to fall with astonishing regularity in the zone between the time when the plantar grasp reflex was last present and the visit where it first was not elicited. This correlation with standing may be due to either or both of the following factors: 1. As cortical function gains control and directs the use of the lower extremities and feet we might logically expect the disappearance of a primitive reflex. 2. The loss of the reflex may be occasioned by the application of sufficiently frequent, physically frustrated, stimuli to the trigger point by applying body weight when the ball of the foot contacts the floor in standing.

It was hoped that examination of older mongolian idiots who have never walked might give a definite answer to this question, in spite of the recognized sluggishness of reflexes in this clinical group. Brain and Curran [20] had reported the demonstration of the plantar grasp reflex in 25 of 42 mongolian idiots (up to 20 years of age). No mention was made of their ability to stand or walk. In only 8 of 13 nonstanding mongols up to 5 years of age (not included in the other statistics of this report) was a plantar grasp reflex demonstrable in irregular to striking degree, and it is thereby apparent that these children will not provide the concise answer we seek.

Observations on the plantar grasp reflex in pathologic conditions are in progress, in the hope that they will reveal some added clinical usefulness of this "residual of phylogenetic function." Brain and Curran have

reported a plantar grasp reflex in older persons with frontal lobe lesions.

Conclusions

Eight hundred fifty-seven periodic observations on a group of 103 normal infants from birth to 1 or 2 years of age appear to warrant the following conclusions:

The spontaneously appearing Babinski sign, which is seen principally in the newborn period, is not a reflection of clinically recognizable pathology.

A Babinski sign, often bilateral, is frequently but irregularly present in the first six months of life; thereafter it is relatively uncommon.

Because the sign appears and disappears, sometimes repeatedly in the same infant, lack of myelinization does not appear to be a rational explanation for its presence in the young infant. Perhaps this phenomenon is distinct from the true Babinski sign.

The plantar grasp reflex is usually present at or soon after birth; it is remarkably constant and active during early infancy, and usually disappears between 6 and 12 months of age.

The disappearance of the plantar grasp reflex appears to be related to the age of standing.

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REFERENCES

1. Parmelee, A. H.: The Management of the Newborn, Chicago, The Year Book Publishers, Inc., 1952.

2. Babinski, M. J.: Sur le Réflexe cutané plantaire dans certaines affections organiques du système nerveux central, Compt. rend. Soc. biol. 3:207-208, 1896.

3. Babinski, M. J.: Du Phénonène des orteils, Semaine méd. 18:321-322, 1898.

4. Wartenberg, R.: The Babinski Reflex After 50 Years, J. A. M. A. 135:763-767 (Nov. 22) 1947.

5. Ford, F. R.: Disease of the Nervous System in Infancy, Childhood and Adolescence, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1952.

6. Spurling, R. G.: Practical Neurologic Diagnosis, Ed. 5, Springfield, Ill., Charles C Thomas, Publisher, 1955.

7. Brain, W. F.: Diseases of the Nervous System, Ed. 4, London, Oxford University Press, 1951.

8. Alpers, B. J.: Clinical Neurology, Philadelphia, F. A. Davis Company, 1946.

9. De Anglis, F.: Reflexes of the New-Born, Am. J. Dis. Child. 26:211-215 (Sept.) 1923.

10. Chaddock, C. G.: A Preliminary Communication Concerning a New Diagnostic Sign, Interstate M. J. 18:742-746 (July) 1911.

11. Gordon, A.: A New Reflex: Paradoxic Flexor; Its Diagnostic Value, Am. Med. 8:971 (Dec. 3) 1904.

12. Oppenheim, H.: Zur Pathologie der Hautreflexe an dem unteren Extremitäten, Monatsschr. Psychiat. u. Neurol. 12:421-423; 518-530, 1902.

13. Halverson, H. M.: Studies on the Grasping Responses in Early Infancy, J. Genet. Psychol. 51:371-446 (June) 1937.

14. McGraw, M. B.: The Neuromuscular Maturation of the Human Infant, Morningside Heights, N. J., Columbia University Press, 1943.

15. Burr, C. W.: The Reflexes in Early Infancy, Am. J. Dis. Child. 21:529-533 (June) 1921.

16. Buchanan, D.: The Child in Health and Disease (Grulee & Eley), Ed. 2, Baltimore, Williams & Wilkins Company, 1952, pp. 783.

17. Richter, C. P.: The Grasping Reflex in the New-Born Monkey, Arch. Neurol. & Psychiat. 26:784-790 (Oct.) 1931.

18. Morse, J. L.: A Study of the Plantar Reflex in Infancy, Pediatrics 11:13-17 (Jan. 1) 1901.

19. Feldman, W. M.: The Nature of the Plantar Reflex in Early Life and the Causes of Its Variation, Am. J. Dis. Child. 23:1-40 (Jan.) 1922.

20. Brain, W. R., and Curran, R. D.: The Grasp Reflex of the Foot, Brain 55:347-356 (Sept.) 1932.

The Role of Hemophilus Influenzae in Respiratory Infections of Premature Infants

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We have recently had an outbreak of respiratory infection in our premature nursery in which we believe that H. influenzae may have had some part as an etiologic agent. The following report is an account of the clinical and bacteriological findings during this outbreak.

Clinical Observations

Three infants were discharged from our premature nursery in good condition on the same day. Their course in the nursery had been uneventful. Four, six, and ten days, respectively, after discharge from the nursery these infants developed signs of respiratory infection. The symptoms rapidly progressed to include marked respiratory distress, with severe paroxysms of coughing and periods of apnea; so all three infants were admitted to the isolation ward of the hospital with a provisional diagnosis of pertussis. These three infants constitute Patients 1, 2, and 3 in this series.

At approximately the same time that these three infants were readmitted to the hospital we noted the first signs of respiratory infection in the babies of the premature nursery from which the three infants had been discharged. There were 27 premature infants in this nursery at this time, and they constitute Patients 4 through 30 in this report. The age of the infants in this series at the onset of the outbreak ranged from 1 to 10 weeks, and their weights were between 1100 and 3100 gm.

We have divided the 30 infants into three groups according to the severity of their symptoms. Group I includes the infants whose symptoms were considered severe. The clinical manifestations in this group consisted of mucopurulent nasal discharge, paroxysms of severe coughing often followed by vomiting, rapid labored respiration with moderate to severe intercostal retraction, and periods of apnea and cyanosis. None of the infants had temperature elevations. There were 11 patients in this group, and they were considered critically ill over a period ranging from five to eight days.

Group II includes the infants who were considered to have mild symptoms consisting of nasal discharge, frequent sneezing, and mild cough. Again, none of the infants in this group had temperature elevations. There were eight infants in this group, and at no time were any of these patients thought to be critically ill.

Group III consists of the remaining 11 infants in the premature nursery, who manifested no obvious clinical symptoms.

Chest x-rays were made on all infants included in Groups I and II. None of the x-rays on the infants in Group II with mild symptoms revealed any abnormality. Six of the eleven considered to have severe symptoms had x-ray evidence of pneumonitis or pneumonitis and atelectasis involving one or more lobes. Examples of these x-ray findings may be seen in Figures 1 and 2.

A large number of the infants in Groups I and II developed, during the course of their illness, a definite, and in some cases a marked, elevation in their white blood cell counts, with a lymphocyte count of 50% to 70%.

The Table provides a summary of the findings in the 30 infants included in this series.

From the Department of Pediatrics, Medical College of Alabama.

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Fig. 1. (Patient 4).—Chest roentgenogram showing bilateral upper lobe pneumonia.

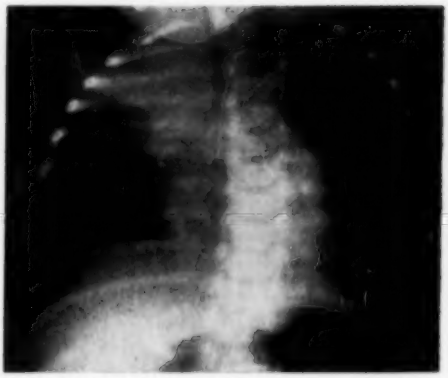

Fig. 2. (Patient 5).—Chest roentgenogram showing pneumonia and atelectasis of right upper, right middle, and left upper lobes.

Since a diagnosis of pertussis was strongly considered on the 3 infants readmitted to the hospital, these infants and also the 27 infants in the premature nursery received hyperimmune pertussis antiserum in a dose of 1 cc. daily for a period of three days. All the infants were also given tetracycline orally, 20 mg. per kilogram of body weight daily. Other therapeutic measures included oxygen, atmosphere with increased moisture content, and parenteral fluids as indicated in the severely ill infants. There were no deaths.

Bacteriological Observations

Nasopharyngeal cultures were obtained on all infants included in this study. Cultures

Outbreak of Respiratory Infection in a Premature Nursery: Summary of Clinical and Bacteriological Findings

Patient	Age, Wks.	Weight, Gm.	Symptoms	White Blood Cell Count	Nasopharyngeal Culture for H. Influenzae	X-Ray Findings
1	7	2,500	Severe	72,000	Positive	...
2	7	2,500	Severe	55,000	Negative	Atelectasis & pneumonia: right upper lobe
3	6	3,100	Severe	13,500	Positive	Negative
4	10	2,100	Severe	7,500	Positive	Bilateral upper lobe pneumonia
5	8	2,380	Severe	31,000	Positive	Atelectasis & pneumonia: right upper lobe, right middle lobe, & left upper lobe
6	4	2,400	Severe	19,000	Positive	Negative
7	4	2,200	Severe	42,000	Positive	Atelectasis & pneumonia: right upper lobe; pneumonia: right lower lobe
8	4	1,460	Severe	22,000	Positive	Negative
9	3	2,460	Severe	7,000	Positive	Pneumonia: right middle lobe
10	3	2,000	Severe	11,000	Positive	Pneumonia: right middle lobe
11	5	2,200	Severe	22,500	Positive	Negative
12	2	2,000	Mild	24,000	Positive	Negative
13	5	2,200	Mild	19,800	Positive	Negative
14	2	2,300	Mild	11,000	Negative	...
15	3	2,000	Mild	13,800	Positive	Negative
16	2	1,800	Mild	...	Negative	Negative
17	2	1,700	Mild	12,000	Positive	Negative
18	2	1,700	Mild	11,800	Positive	Negative
19	3	1,600	Mild	10,000	Positive	Negative
20	2	1,580	None	18,000	Negative	...
21	1	1,860	None	11,000	Negative	...
22	1	1,900	None	11,000	Negative	...
23	1	1,100	None	6,500	Negative	...
24	2	2,000	None	14,500	Positive	...
25	5	2,500	None	7,000	Positive	...
26	6	2,400	None	11,000	Positive	...
27	3	2,400	None	15,400	Positive	...
28	2	2,400	None	9,000	Positive	...
29	3	1,900	None	12,000	Negative	...
30	2	1,600	None	11,000	Negative	...

were inoculated on blood agar, chocolate agar, and Bordet-Gengou agar plates. The results of these cultures revealed variable growth of staphylococci, diphtheroids, and coliform organisms. None of the cultures were positive for pneumococci, β-hemolytic streptococci, Hemophilus pertussis, or Hemophilus parapertussis.

The only consistent observation was the isolation of H. influenzae from the nasopharynx of 21 of the 30 infants. This organism was identified by colony characteristics, morphology, and staining reaction by Gram's method; by growth requirements for the X and V factors, and by the quellung reaction with type-specific H. influenzae antiserum * when possible. Fresh antiserum was unavailable at the onset of this outbreak, and by the time it was obtained we were able to type only eight of the cultures of H. influenzae isolated. These eight were found to be Type b. Repeat nasopharyngeal cultures were negative for H. influenzae in a majority of the infants after 48 hours of therapy, and none were positive after 96 hours. A tabulation of the infants who had nasopharyngeal cultures positive for H. influenzae is found in the Table.

Blood serum was obtained from each infant in this series during the acute stage of the disease and again 10 to 15 days later. These sera were tested for the presence of antibodies against H. influenzae Types a and b by the slide agglutination technique as described by Wood, Buddingh, and Abberger [2] and also by the hemagglutination technique described by Warburton and Keogh.[5] We were unable to demonstrate the presence of antibody in any of the sera by the two methods employed.

An attempt to locate the source of infection included making nasopharyngeal cultures on all personnel who had any contact with the premature nursery. None of these cultures were positive for H. influenzae, and we therefore have no known source of infection.

* Supplied by Dr. Sarah Woods, Department of Pediatrics, Vanderbilt University School of Medicine, and Dr. G. J. Buddingh, Department of Microbiology, Louisiana State University School of Medicine.

Comment

The role of Hemophilus influenzae as the etiologic agent in cases of meningitis, obstructive infections of the respiratory tract, osteomyelitis, and pyarthrosis occurring in patients of the pediatric age group is well established. Nyhan, Rectanus, and Fousek,[1] in 1955, reviewed the problem of H. influenzae Type b as a cause of primary pneumonia in children, and Wood, Buddingh, and Abberger [2] have presented bacteriologic and serologic evidence suggesting that H. influenzae Types a and b may have some role in the pathogenesis of acute bronchiolitis of infants.

Published reports of H. influenzae infections in premature infants are rare. Dunham [3] lists this organism as a cause of pneumonia in premature infants. Clifford [4] refers to the recovery of H. influenzae from 3 cases out of a series of 57 premature infants who died after the first seven days of life. The site of the infection in these three instances is not stated.

Fothergill and Wright [6] have shown that the age incidence of H. influenzae meningitis is closely related to the bactericidal power of the blood, and, as pointed out by Alexander,[7] most severe H. influenzae infections, with the exception of the typical obstructive infections of the respiratory tract, probably follow the same age incidence pattern. Although no premature infants were included in the studies of Fothergill and Wright, the work of Dancis and Kunz [8] indicates that the bacteriostatic activity of serum from premature infants is very similar to that of full-term infants. The steady fall in the γ-globulin levels of premature infants during the first few weeks of life as reported by Norton, Kunz, and Pratt [9] coincides with the decrease in the bacteriostatic activity referred to above.

It is interesting to note that 9 of the 11 infants who had severe symptoms were 4 weeks of age or older, whereas only 3 of

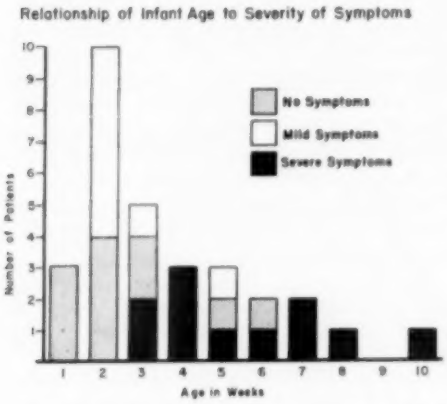

Fig. 3.—Relationship of infant age to severity of symptoms.

the 19 with mild or no symptoms were in this age group. This is graphically illustrated in Figure 3. Although the number of infants included in this report is certainly too small to draw any conclusions of statistical significance, the age of the infants in relation to the severity of symptoms would seem to support the idea that the newborn premature receives some protection against H. influenzae from the mother by way of the placenta and that this protection is lost fairly rapidly after birth. This relationship of the age of the infants to the severity of symptoms may also have been associated with the length of incubation period; that is, the older infants, with a longer incubation period before treatment was instituted, manifesting more severe symptoms and the younger infants, with a shorter time lapse before therapy was started, exhibiting either mild or no symptoms.

The failure to demonstrate antibody formation as evidenced by our inability to show agglutination is disappointing but not too surprising. By the use of the hemagglutination technique of Stulberg and Zuelzer [10] were able to demonstrate a rise in antibody titer against Escherichia coli $0127:B_8$ in 13 out of a total of 40 premature infants with diarrhea caused by this organism. There are several factors which may have accounted for our inability to demonstrate antibody. These include the ability of the premature infant to produce antibody in detectable amounts, the period of time at which the sera were collected, and the eradication of the organism, and thus the antigenic stimuli, by use of antibiotics.

Finally, the isolation of H. influenzae from the nasopharynx of the infants included in this report is certainly not positive evidence that this organism was the sole or indeed a contributing cause of the symptoms manifested. The possibility of a viral agent either alone or in conjunction with H. influenzae as an etiological agent was not investigated. The rather consistent presence of H. influenzae, its disappearance during appropriate therapy, and the clinical improvement following therapy lead us to believe that this organism did indeed play some role in the pathogenesis of the respiratory symptoms in this group of premature infants.

Summary

We present the clinical and bacteriological findings in an outbreak of respiratory infections involving 30 infants in our premature nursery. Eleven of these infants developed severe respiratory symptoms, with paroxysms of coughing, vomiting, marked retraction, and periods of apnea. Eight infants had mild symptoms of coughing, sneezing, and mucopurulent nasal discharge, and the remaining 11 infants had no clinical symptoms.

H. influenzae was isolated from the nasopharynx of 21 of the 30 infants. Sera from the infants at acute and convalescent stages failed to show the presence of antibodies against H. influenzae with use of the slide agglutination and hemagglutination techniques.

All the infants were treated with tetracycline, hyperimmune pertussis antisera, and supportive measures, and all recovered.

We feel that this represents an outbreak in a premature nursery of respiratory infections in which H. influenzae probably played some role in the pathogenesis.

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REFERENCES

1. Nyhan, W. L.; Rectanus, D. R., and Fousek, M. D.: Hemophilus Influenzae Type b Pneumonia, Pediatrics 16:31-42 (July) 1955.

2. Wood, S. H.; Buddingh, G. J., and Abberger, B. F.: An Inquiry into the Etiology of Acute Bronchiolitis of Infants, Pediatrics 13: 363-372 (April) 1954.

3. Dunham, E. C.: Premature Infants: A Manual for Physicians, Ed. 2, New York, Paul B. Hoeber, Inc., 1955, p. 244.

4. Clifford, S. H.: Infections of the Newborn and Premature Infant, Pennsylvania M. J. 53:25-31 (Jan.) 1950.

5. Warburton, M. F., and Keogh, E. V.: A Hemagglutination Test for the Diagnosis of Influenzal Meningitis, M. J. Australia 1:135-137 (Jan. 29) 1949.

6. Fothergill, L. D., and Wright, J.: Influenzal Meningitis: The Relation of Age Incidence to the Bactericidal Power of Blood Against Causal Organism, J. Immunol. 24:273-284 (April) 1933.

7. Alexander, H. D.: Influenza Bacillus Infections, in Holt Pediatrics, Ed. 12, edited by L. Emmett Holt Jr. and Rustin McIntosh, New York, Appleton-Century-Crofts, Inc. 1953, p. 1201.

8. Dancis, J., and Kunz, H. W.: Studies of the Immunology of the Newborn Infant, Pediatrics 13:339-345 (April) 1954.

9. Norton, P. M.; Kunz, H., and Pratt, E. L.: Electrophoretic Analysis of Serum Protein in Premature Infants, Pediatrics 10:527-532 (Nov.) 1952.

10. Stulberg, C. S., and Zuelzer, W. W.: Infantile Diarrhea Due to Escherichia Coli, Ann. New York Acad. Sc. 66:90-99 (Aug.) 1956.

Meprobamate in the Treatment of Epilepsy of Children

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Recurrent convulsive seizures (epilepsy) are among the most persistent and perplexing of childhood disorders. We assign the term "minor motor" to the attacks that appear initially in early life, usually between 3 and 12 months of age, occur almost entirely in the presence of organic brain damage, and are clinically manifested as (1) the akinetic type, in which there is a sudden nod or dropping of the head, usually forward, or an abrupt loss of muscular control, resulting in a precipitous fall; the patient is usually able to rise almost immediately but may appear disoriented for several minutes thereafter, and (2) the massive myoclonic type, which is characterized by a variety of clinical symptoms but most frequently consists of a sudden bending of the head with simultaneous extension of the upper extremities and flexion of the thighs upon the abdomen, accompanied by a cry.

The electroencephalogram frequently indicates the presence of abnormalities, which have been referred to by Gibbs and coworkers [1,2] as "hypsarhythmia" (mountainous arrhythmia). The pattern is characterized by very high voltage; random, slow waves, and one- to two-per-second spike discharges in all cortical areas, which vary from moment to moment in duration and location, occasionally are generalized, but are never rhythmically repetitive nor highly organized.

Treatment of the patient with minor motor seizures remains a baffling problem. Spells of this type are the most difficult of all epileptic seizures to control. None of the anticonvulsant drugs have proved very helpful. We have obtained good results in a few patients with phenobarbital, mephobarbital (Mebaral), metharbital (Gemonil), bromides, phensuximide (Milontin), and methsuximide (Celontin). The ketogenic diet, however, has been most satisfactory in our experience. We have managed approximately 350 children suffering from minor motor epilepsy on this regimen and have achieved complete control of seizures in about 50%.

Of great importance and equally frustrating is regulation of the behavior disorders (hyperirritability, hyperactivity, belligerence, and short attention span) [3-5] frequently encountered in epileptic children, which in many cases are much more of a problem to the parents than are the seizures themselves. Whereas convulsive episodes occur relatively infrequently (as weekly or monthly), these behavior disorders are present almost continously and contribute to the difficulties of management. In some of our patients such disturbances are so pronounced as to necessitate institutionalization. This stereotyped behavior pattern is not limited to epileptics but also develops in some patients following encephalitis and other conditions that result in cerebral damage, may occur in so-called idiopathic as well as in secondary epilepsy, and, although most frequently found in retarded children, may be seen in those with normal intelligence as well. Similar disorders may be associated with use of anticonvulsants, particularly phenobarbital.

Meprobamate,* 2-methyl-2-*n*-propyl-1, 3-propanediol dicarbamate,[6] a compound chemically related to mephenesin, appeared to offer some possibility of effectiveness against minor motor seizures. Reported as

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* Meprobamate is available as Equanil (Wyeth Laboratories, Inc.) and as Miltown (Wallace & Tiernan Inc.).

the most potent anticonvulsant of a series investigated by Berger,[7] this agent has been described by various other investigators as effective for relief of anxiety and tension states,[8-11] tension headaches, [9-13] behavior problems,[10,11] and psychoses [8-12] and for relaxation of emotional and muscular tension in cerebral palsy.[14-16]

The first clinical use of meprobamate for treatment of epilepsy was described by Perlstein,[14] in 1956. He reported "moderate" to "marked" benefit in 15 (83%) of 18 patients with "idiopathic petit mal" and in 5 (33%) of 15 patients with "organic petit mal." He found that the compound was less effective in "organic grand mal" and least helpful in "idiopathic grand mal." Perlstein also observed that in many of his patients with grand mal the attacks were made worse.

It appears that the seizures Perlstein described as "idiopathic petit mal" are those we classify as petit mal spells (three-per-second spike and wave dysrhythmia) and the ones he calls "organic petit mal" are those we designate as minor motor.

Baird and Borofsky [17] observed definite improvement under meprobamate medication in 14 (61%) of 23 children with "infantile myoclonic spasms." These spells are similar to the type we classify as massive myoclonic minor motor seizures. After failure of treatment with other agents, their patients received meprobamate (the maximum dose was 2400 mg. daily), either alone or in combination with phenobarbital and diphenylhydantoin (Dilantin), for 1 to 18 months.

Plan of Study

Meprobamate was administered to 128 children, aged 11 months to 14 years, who suffered from various types of epilepsy (major motor, petit mal, minor motor, and psychomotor seizures).

Forty-two (33% of the entire series) had never been treated previously with anticonvulsants. These patients received only meprobamate throughout the study.

Eighty-six (67% of the series) had received one or more anticonvulsants (phenobarbital, mephobarbital, diphenylhydantoin, primidone [Mysoline], methoin [Mesantoin], trimethadione [Tridione], paramethadione [Paradione], phensuximide, or acetazolamide [Diamox]) in maximum dosage for six months or more before start of this investigation. In 55 (64%) of this group the previous anticonvulsant medication reduced the frequency or severity of the seizures to some extent but failed to control them completely. In the remaining 31 (36% of the group) previous anticonvulsant therapy had been completely ineffectual.

The 64% (55 patients) of the previously treated group who had responded in some degree to anticonsulvants received meprobamate in addition to the original medication, in the dosage previously used, throughout the entire observation period. Many of them received maximum dosages of phenobarbital and diphenylhydantoin in conjunction with meprobamate. The 36% (31 patients) whom previous medication had not benefited received meprobamate in addition to the same dosage of anticonvulsants originally used, for the first month of study. During the next two months the previous medication was gradually withdrawn. Thereafter, this segment of the group received meprobamate only.

Seventy-six (59%) of the entire series also exhibited the stereotyped behavior disorders commonly observed in epileptic children.

Dosage.—Meprobamate is dispensed in 400 mg. tablets. The total daily dosage employed in this study varied from 400 mg. to 2400 mg. (Table 1) and was administered in two to four divided doses. The amount was increased every two weeks, at the rate of 200 mg. (½ tablet) daily, as necessary, to the maximum dose employed.

Medication was continued from nine months to two years. Eighty-nine (70%) received the compound continously for at least one and one-half years.

Routine blood cell counts and urinalyses were performed monthly on all 128 patients for the entire period of medication.

Results

Minor Motor Epilepsy.—Meprobamate was of value only for treatment of minor motor seizures (Tables 2-4).

Attacks were controlled completely in 2 of the 14 patients who had not been treated previously with any type of anticonvulsant

TABLE 1.—*Dosage of Meprobamate for Treatment of 128 Epileptic Children*

Age, Yr.	Initial Dosage, Mg.	Maximum Dosage, Mg.
Less than 3	200 twice daily	400 three times daily
3 to 6	200 three times daily	400 four times daily
6 to 14	400 twice daily	600 four times daily

TABLE 2.—*Results in Forty-Two Patients Who Had Not Been Treated Previously with Any Form of Anticonvulsant Therapy* *

Type of Seizure	Patients, No.	Effect of Meprobamate on Seizures			
		Complete Control	Pronounced Improvement	Improvement in Some Degree	No Effect
Major motor (grand mal)	8	0	0	0	8
Pure petit mal	9	0	0	0	9
Psychomotor	5	0	0	0	5
Minor motor	14	2	1	1	10
Mixed (major motor and petit mal)	2	0	0	0	2
Mixed † (major motor and minor motor)	4	0	1	1	2
Total	42	2	2	2	36

* Patients receiving only meprobamate throughout observation period.
† Only minor motor seizures were favorably affected.

agent and who received only meprobamate throughout the entire period of therapy (Table 2). One patient showed pronounced improvement, and one showed improvement in less degree.

In the 18 patients in whom the frequency of attacks had been partially reduced with maximum dosages of other anticonvulsants, minor motor seizures were completely controlled in 3 on addition of meprobamate to the previous regimen (Table 3). Two showed pronounced improvement, and one was improved to some extent.

Minor spells were controlled completely in one of the nine patients who had been entirely refractory to maximum dosages of other anticonvulsants and who, for the first month of the study, received both the previously ineffective medication, in the same dosage, and meprobamate; then, after gradual withdrawal of the original medication in the subsequent two months, the patients were given meprobamate alone (Table 4). Two others showed improvement in some degree.

None of the patients with other types of seizures (major motor, petit mal, or psychomotor) were significantly benefited by the compound. In a few of the patients with petit mal epilepsy there was a temporary reduction (for several months or so) in the frequency of the attacks. However, in none of them did the improvement last longer than three months. The frequency of major motor seizures was increased in three patients, especially when the larger doses of meprobamate were administered.

There was no indication of incompatibility with other anticonvulsants, nor of potentiation of the common sedative effects of such agents.

Behavior.—Of the 76 children whose behavior problems caused difficulty in management, 32 (42%) showed definite im-

TABLE 3.—*Results in Fifty-Five Patients Whose Seizures Were Controlled Partially with Maximum Dosages of Other Anticonvulsant Drugs* *

Type of Seizure	Patients, No.	Effect of Meprobamate on Seizures			
		Complete Control	Pronounced Improvement	Improvement in Some Degree	No Effect
Major motor (grand mal)	10	0	0	0	10
Pure petit mal	12	0	0	0	12
Psychomotor	6	0	0	0	6
Minor motor	18	3	2	1	12
Mixed (major motor and petit mal)	4	0	0	0	4
Mixed (major motor and psychomotor)	2	0	0	0	2
Mixed † (major motor and minor motor)	3	0	1	1	1
Total	55	3	3	2	47

* Patients receiving meprobamate in addition to same dosage of previous medication throughout observation period.
† Only minor motor seizures were affected favorably.

TABLE 4.—*Results in Thirty-One Patients Whose Seizures Were Completely Refractory to Maximum Dosages of Other Anticonvulsant Drugs* *

Type of Seizure	Patients, No.	Effect of Meprobamate on Seizures			
		Complete Control	Pronounced Improvement	Improvement in Some Degree	No. Effect
Major motor (grand mal)	7	0	0	0	7
Pure petit mal	7	0	0	0	7
Psychomotor	4	0	0	0	4
Minor motor	9	1	1	1	6
Mixed (major motor and petit mal)	2	0	0	0	2
Mixed (major motor and psychomotor)	1	0	0	0	1
Mixed † (major motor and minor motor)	1	0	1	0	0
Total	31	1	2	1	27

* During first month patients were given meprobamate in addition to same dosage of previous medication; during subsequent two months previous medication was gradually withdrawn; thereafter, only meprobamate was given.
† Only minor motor seizures were affected favorably.

provement, with control of restlessness and reduction in irritability. Meprobamate, in our hands, proved of greater value for alleviation, at least in part, of the hyperactivity and emotional disturbances of these children than had reserpine (Serpasil) or chlorpromazine (Thorazine).

Side-Effects.—With the exception of drowsiness in a few patients, no significant side-actions occurred. One patient experienced diarrhea each time the compound was administered.

Throughout treatment no abnormalities developed in the blood picture. The results of urinalyses remained within normal limits.

Comment

The results obtained in this study and also those reported by Perlstein [14] and Baird and Borofsky [17] indicate that meprobamate is of some worth for treatment of minor motor seizures—of all types of epilepsy, the least susceptible to anticonvulsive therapy. Although it is true that complete control of the attacks was achieved in but a small number, nevertheless, any agent that can afford relief in some measure, if only in a few patients, is of definite benefit.

A very valuable property is the tranquilizing action exerted by the compound on the emotional reactions of the patient, so that hyperactivity and other behavior problems are alleviated.

One of the great advantages of meprobamate is the apparently complete freedom from untoward side-actions, which is so important in the long-term medication required in epileptic patients. To our knowledge, no irreversible toxic reactions have been observed as a result of administration of this compound.

Summary

One hundred twenty-eight epileptic children, of whom 59% also manifested hyperactive behavior disorders, were treated with meprobamate for periods ranging from nine months to two years. The maximum dosage of one or more other anticonvulsants, administered for periods of six months or more, had previously proved ineffective in controlling seizures in 86 (67%) of these patients.

Meprobamate controlled or reduced minor motor seizures in 4 of 14 patients not previously treated with anticonvulsant drugs, in 6 of 18 patients whose condition was partially controlled by other drugs, and in 3 of 9 patients in whom the disease was completely refractory to maximum dosage of other anticonvulsants.

Behavior difficulties were alleviated in 42% of 76 patients in whom disorders of this type were present.

Patients with major motor, petit mal, or psychomotor seizures were not significantly relieved.

No side-actions of consequence were observed.

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REFERENCES

1. Gibbs, E. L.; Fleming, M. M., and Gibbs, F. A.: Diagnosis and Prognosis of Hypsarhythmia, Pediatrics 13:66-73, 1954.

2. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography: Vol. 2. Epilepsy, Cambridge, Mass., Addison-Wesley Press, Inc., 1952.

3. Bradley, C.: Behavior Disturbances in Epileptic Children, J. A. M. A. 146:436-441, 1951.

4. Gettinger, L., Jr.: The Relationship of Epilepsy and Hyperactive Behavior Problems, Epilepsia 2:148, 1953.

5. Ounsted, C.: The Hyperkinetic Syndrome in Epileptic Children, Lancet 2:303-311, 1955.

6. Berger, F. M.: The Pharmacological Properties of 2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate (Miltown), a New Interneuronal Blocking Agent, J. Pharmacol. & Exper. Therap. 112:413-423, 1954.

7. Berger, F. M.: Meprobamate, Its Pharmacologic Properties and Clinical Uses, Internat. Rec. Med. 169:184-196, 1956.

8. Borrus, J. C.: Study of Effect of Miltown (2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate) on Psychiatric States, J. A. M. A. 157:1596-1598, 1955.

9. Lemere, F.: New Tranquilizing Drugs, Northwest Med. 54:1098-1100, 1955.

10. Selling, L. S.: Clinical Study of a New Tranquilizing Drug: Use of Miltown (2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate), J. A. M. A. 157:1594-1596, 1955.

11. Selling, L. S.: A Clinical Study of Miltown, a New Tranquilizing Agent, J. Clin. & Exper. Psychopath. 17:7-14, 1956.

12. Thal, N.: Premedication for Electroshock Treatment, Dis. Nerv. System 17:3-8, 1956.

13. Friedman, A. P.: Use of Tranquilizers in the Treatment of Headache, Am. Pract. & Digest Treat. 8:94-97, 1957.

14. Perlstein, M. A.: Use of Meprobamate (Miltown) in Convulsive and Related Disorders, J. A. M. A. 161:1040-1044, 1956.

15. Gillette, H. E.: Relaxant Effects of Meprobamate in Disabilities Resulting from Musculoskeletal and Central Nervous System Disorders: Clinical Observation of 55 Cases, Internat. Rec. Med. 169:453-68, 1956.

16. Gillette, H. E.: Effect of Meprobamate on Cerebral Palsy: Electromyographic Studies on Patients with Pyramidal or Extrapyramidal Lesions, read before the Conference on Meprobamate and Other Agents Used in Mental Disturbances, The New York Academy of Sciences, Sections on Biology and Psychology, New York, Oct. 18-19, 1956; Tr. New York Acad. Sc., to be published.

17. Baird, H. W., III, and Borofsky, L. G.: Infantile Myoclonic Seizures, J. Pediat. 50:332-339, 1957.

Acute Adrenal Insufficiency Due to Congenital Defect

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Transient adrenal insufficiency in early infancy has been described by Jaudon.[1] Congenital hypoplasia as the cause of fatal adrenal failure is the least understood condition among the various etiological possibilities. The following study may be contributory to the understanding of the pathology of this rare condition and of the interrelation between the electrolyte-controlling mechanism and the histopathological changes of the adrenal cortex.

Report of Case

A white boy weighing 8 lb. 12 oz. at birth began vomiting, having diarrhea, and losing weight at the age of 2 weeks and was admitted to the hospital a week later in severe shock with diarrhea and dehydration. The skin was grayish, and the child appeared lethargic. The weight was 13 oz. below the birth weight. The genitalia were normal. A slight trace of albumin was found in the urine; tests for sugar and sediment were negative. Blood chemistry studies showed sodium, 120 mEq. per liter; potassium, 10 mEq. per liter; chloride, 110.9 mEq. per liter; CO_2, 21.5 mEq. per liter; 17-ketosteroids, 0.6 mg. in 24 hours (determined according to Reddy[2]). Despite intravenous fluid therapy with an average of 150 cc. isotonic sodium chloride, 500 cc. 10% invert sugar in water, and 50 cc. ⅙ M sodium lactate in 24 hours, the child did not maintain hydration or electrolyte balance. After treatment with 15 mg. of cortisone acetate daily and 0.5 mg. of desoxycorticosterone acetate t. i. d. the child began to recover. Cortisone was discontinued and desoxycorticosterone acetate was replaced by the long-acting preparation desoxycorticosterone (Percorten) trimethylacetate (Ciba), with the oral administration of extra sodium chloride.

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After 26 days of treatment the weight increased to 10 lb. 5 oz. Thirty days after the previous injection the patient received another one of the long-acting drug. The electrolytes at this time were: sodium, 133 mEq. per liter; potassium, 4.7 mEq. per liter; chloride, 104 mEq. per liter, and CO_2, 20 mEq. per liter.

At the age of 3 months, five days after the second injection of the long-acting drug, the baby suddenly went into shock and was readmitted to the hospital in peripheral collapse. Temperature was 99.6 F; pulse rate, 176; respiration rate, 104. The heart sounds were poor and muffled. The liver was palpable 4 fingerbreadths below the costal margin. Blood chemistry studies showed sodium, 135 mEq. per liter; potassium, 5.6 mEq. per liter; chloride, 112 mEq. per liter; CO_2, 16 mEq. per liter. WBC count 25,000, with a shift to the left. In spite of immediate administration of intravenous dextrose and saline, a blood transfusion, and digitalis the baby died six hours after admission. There were terminal twitchings of the extremities. Although cardiac failure was present, in view of the previous history the terminal picture seemed more in keeping with adrenal failure. The cardiovascular findings at autopsy were not considered severe enough to completely explain the collapse.

*Pathology.**—The most significant finding at autopsy involved the adrenal glands. They lay in their regular position but were extremely small, weighing together 1 gm. Each was yellow throughout, lobated, and moderately firm. On histological examination one could identify a cortex and medulla; the latter was small and composed of collections of immature paraganglionic cells characteristic for this age. The cortex was unusual. It was composed of one type of cell having features in common with those of the fetal adrenal. The entire cortical area was occupied by eosinophilic cells of varying shape and size (Fig. 1). Many of these were several times larger than normal (Fig. 2). Some of the cells were arranged in columns, but many lay haphazardly in small groups separated by sinuses. The cytoplasm of the prevailing cell was granular, acidophilic, and often vacuolated. Few contained intracytoplasmic droplet-like inclusions. The nuclei varied in size and in staining, but the nucleus-cytoplasm ratio remained

* The autopsy was performed by Drs. J. McGovern and H. E. MacMahon.

fairly constant. Large cells generally possessed large nuclei, and more often than not the nucleus was displaced to one side. Some cells had prominent nucleoli, but no mitoses were found. In the central area isolated cortical cells were fragmented, poorly defined, and showed lysis of both nucleus and cytoplasm. A very occasional group of cells in this area was necrotic and calcified. There was no division of the cortex into zones. There was no peripheral permanent cortex made up of small basophilic cells arranged in compact orderly rows, as is normally found at this age. There were no signs of recent inflammation, and, lastly, a very careful search failed to reveal any accessory adrenal tissue. In summary, the picture was one of hypoplasia of both adrenals in which the cortex, composed of persistent atypical fetal cells, showed both defective growth and arrested maturation.

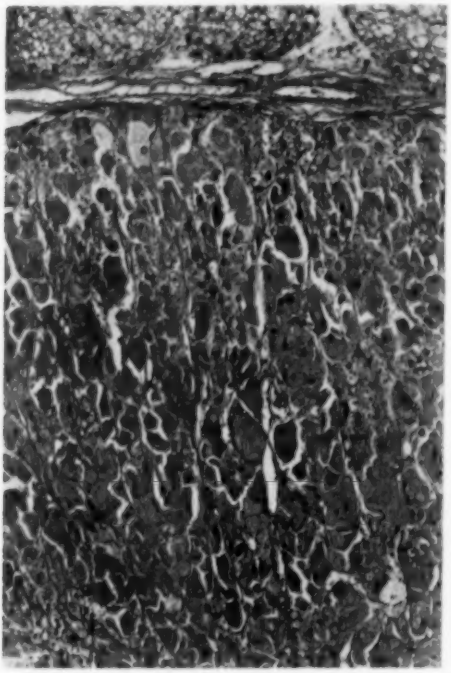

Fig. 1.—Section of adrenal cortex together with capsule and little bordering fetal fat. A uniform pattern of large pleomorphic granular eosinophilic cells crudely arranged in trabeculae and separated by endothelial lined sinuses comprises the cortex. (Note that the permanent definitive cortex, normally composed of a layer of small uniform cells bordering the capsule, is conspicuously absent.) Reduced about 40% from mag. × 100.

Additional but relatively minor findings in the examination of the body at autopsy included a moderate degree of coarctation of the aorta with secondary hypertrophy of the left ventricle, a widely patent foramen ovale, and an abnormally long mesentery to the terminal ileum and ascending colon.

Comment

We are dealing here with a very small adrenal gland composed for the most part of very large cells, a picture that is quite different from the miniature adrenals that one so commonly associates with the anencephalic state. The cells differ from those seen in the adrenals of children suffering from Addisonian symptoms in association with the adrenogenital syndrome. Moreover, they differ from those associated with Cushing's and from those found in

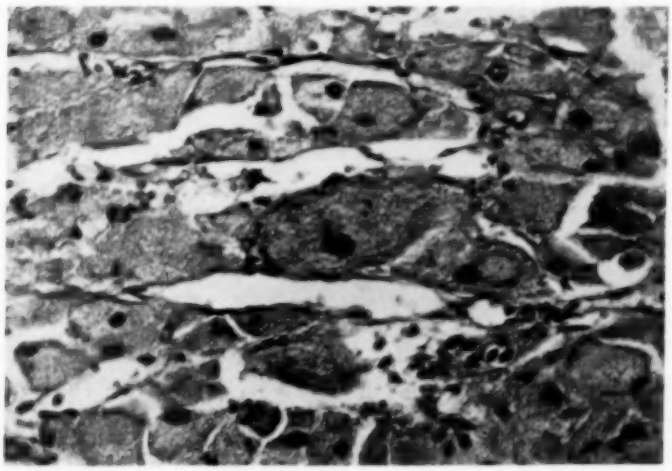

Fig. 2.—A field from the adrenal cortex under higher magnification to show very large cells, pleomorphism of cells, and variation in size and staining of nuclei.

Albright's syndrome. Actually, at first glance they resemble more closely the cells of pleomorphic cortical adenomas. However, in this case what is as important as the presence of atypical cells is the conspicuous absence of a definitive or permanent peripheral cortex.

It is of interest that this child showed a generalized lymphoid hyperplasia, a hyperplasia of interstitial cells of the testes, and moderate colloid retention in the thyroid—findings that have been described in association with diminished cortical activity.

Finally, it should be pointed out that, in addition to the anomaly involving the adrenal glands, there were a moderately severe coarctation of the aorta with secondary hypertrophy of the heart, a widely patent foramen ovale, and a defect in the development of the mesentery leading to a classical example of "cecum mobile."

Whether or not the pattern or character of the cells of the adrenal cortex of this infant were altered by therapy must at this time remain unanswered. Unfortunately, permission to examine the head was not granted, and so neither the brain nor the pituitary were available for study.

The history and course of the adrenal defect in this case is of more than casuistic interest. They bear important relations to the physiology of the adrenal cortex or, more specifically, to only one of the three zones of the cortex, which can almost be considered as three organs in one. The deficiency was exclusively restricted to the electrolyte-controlling function of the cortex and could be temporarily compensated by replacement treatment with desoxycorticosterone acetate. The anatomical finding of a defect of the zona glomerulosa explains the clinical picture satisfactorily. The sugar-controlling mechanism was functioning adequately.

It is hard to explain how the child was able to hold his own during the first 2 weeks of life, in spite of the reduction of the adrenal weight from 5 or 6 gm. to less than 1 gm. There is no indication that a postnatal involution took place; the histopathological picture is not in favor of this interpretation. It may be that the demand on the cortex in the newborn period is so small that the defect manifests itself only later in infancy. The other congenital defect, the coarctation of the aorta, had the significance of syntropy in carriers of multiple congenital defects.

Similar observations have been reported in the literature by several investigators. Kampmeier [2] found the giant cells in the adrenal cortex of 2- to 3-month-old human fetuses. There was retardation or cessation in their multiplication, while the growth and enlargement of the remainder of the gland progressed. Craig and Landing [3] called attention to "anaplastic cells" in the adrenal cortex, which were thought to be the progeny of large single cells found early in the developing fetal cortex. The atypism of the cells is considered by the authors inherent, and not a degenerative phenomenon related to the involutionary changes in the fetal cortex. Recently, Beatty and Hawes [4] discussed the picture of cytomegaly of the adrenal cortex and considered it a distinct entity. They found various other congenital anomalies associated with the adrenal defect. The presence of inclusion bodies within the cytomegalic cells and the associated congenital anomalies were suggestive of a possible viral etiology. The true morbidity is not known.

Summary

A histopathological picture of the adrenal cortex is described, characterized by the absence of a well-defined zona glomerulosa. The cortex was composed almost exclusively of atypical large cells. There was no demonstrable inner or reticular zone. The combined weight of the adrenals was just 1 gm. The picture is different from that of the miniature adrenals in anencephalics and also from that seen in the adrenals of children suffering from Addisonian symptoms in association with the adrenogenital syn-

drome and from that found in Cushing's or Albright's syndrome.

The clinical picture was that of acute adrenal failure, and death occurred in shock. The manifestations in vivo were those of an exclusive failure of the electrolyte-controlling function of the adrenal cortex consistent with an absence of the zona glomerulosa. The defect could be temporarily compensated by replacement therapy with desoxycorticosterone acetate.

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REFERENCES

1. Jaudon, J. C.: Hypofunction of Adrenals in Early Life, J. Pediat. *29*:696, 1946.

2. Kampmeier, O. F.: Giant Epithelial Cells of the Human Fetal Adrenal, Anat. Rec. *37*:95, 1927.

3. Craig, J. M., and Landing, B. H.: Anaplastic Cells of Fetal Adrenal Cortex, Am. J. Clin. Path. *21*:940, 1951.

4. Beatty, E. C., Jr., and Hawes, C. R.: Cytomegaly of the Adrenal Gland, A. M. A. Am. J. Dis. Child. *89*:463, 1955.

5. Reddy, W. J.: Modification of the Reddy-Jenkins-Thorn Method for the Estimation of 17-Hydroxycorticoids in Urine, Metabolism *3*:489, 1954.

Narcotic Withdrawal Reactions in the Newborn

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The medical literature contains relatively little concerning narcotic withdrawal reactions in the newborn. Early case reports were published by Pettey,[1] who described six cases, and Menninger-Lerchenthal.[2] Other case reports have appeared sporadically in foreign journals, but there have been very few in the last 20 years. The early authors seem to have been more concerned with moral, philosophical, and psychiatric aspects of the subject than with the clinical syndrome itself. Goodfriend et al.[3] recently reviewed the literature and described 10 additional cases; however, this article appeared in an obstetrical journal and may have been overlooked by pediatricians. These authors summarized the symptoms of narcotic withdrawal reactions in the newborn and expressed the opinion that the condition probably occurs more frequently than published reports would indicate. Their findings suggested that the symptom complex bears a distinct relationship to the duration of addiction in the mother, the quantity of drug used, and the time of the last dose of narcotic prior to birth of the child. They stressed the importance of early diagnosis and recommended treatment with opiates and/or barbiturates.

There appear to have been virtually no publications on this subject in the American pediatric literature. It is, therefore, the purpose of this paper to report three cases observed at the Boston City Hospital during a period of 14 months, in order to stress to pediatricians the peculiar symptomatology of narcotic withdrawal reactions in the newborn.

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Report of Cases

CASE 1.—A 5 lb. 3 oz. girl was born on Dec. 11, 1955, to a 23-year-old secundigravida. The mother was known to have been a heroin (diacetylmorphine) addict, having taken the drug intravenously periodically for at least four years. The last dose was taken approximately 72 hours prior to delivery. She was admitted 45 minutes prior to delivery with chills, vomiting, and ruptured membranes. No abnormalities were noted in the infant at the time of delivery. When admitted to the nursery, 45 minutes later, the infant was noted to be hyperirritable, showed trembling of all extremities, and had a high-pitched piercing continuous cry. Physical examination was otherwise unremarkable. These findings persisted for five days, after which they abated spontaneously, no treatment having been given. Food intake was fair during this time, with no vomiting, and the infant gained weight. The mother developed mild withdrawal symptoms, which were treated with barbiturates.

CASE 2.—A 6 lb. 3 oz. girl was born on Feb. 1, 1956, to a 22-year-old primigravida. The mother was known to have been a heroin addict for at least two years, taking the drug intravenously. Her last dose was taken 32 hours prior to delivery. She was admitted eight hours prior to delivery in active labor with ruptured membranes. The infant was noted to have a high-pitched cry and to be hyperirritable at the time of delivery. Twenty-four hours later generalized twitching involving all extremities was noted, which interfered with feedings. These findings persisted for six days, after which they abated spontaneously, no treatment having been given. During this period the infant had a poor food intake and vomited frequently. The mother developed severe withdrawal symptoms 48 hours post partum which culminated in status epilepticus and massive gastrointestinal hemorrhage. She was treated with intravenous meperidine (Demerol), chlorpromazine (Thorazine), and phenobarbital; diphenylhydantoin (Dilantin) by rectum, and blood transfusions. She recovered on the 7th postpartum day and was discharged on the 11th postpartum day.

CASE 3.—A 5 lb. 6 oz. boy was born on Feb. 7, 1957, to a 23-year-old trigravida secundipara mother. She was not known to be a drug addict and had had no prenatal care. She was admitted

one hour before delivery with hypertension, albuminuria, and hyperactive reflexes. In view of these signs of toxemia she was treated with intramuscular meperidine, phenobarbital, and magnesium sulfate. Spinal anesthesia was used for delivery, and preanesthetic medication included an additional dose of meperidine, levallorphan (Lorfan), and atropine. The baby showed no abnormalities at the time of delivery. On routine examination at the age of 3 hours he was noted to be hyperirritable, with a depressed Moro reflex and a normal cry. At age 18 hours, he was noted to have a high-pitched piercing continuous cry, irritability was increased, and there were numerous scratch marks on his face. At age 28 hours examination showed generalized clonic movements, including the facial muscles and approaching convulsive intensity, and the same high-pitched cry previously noted. There were neurological signs suggestive of hypocalcemic tetany, and this diagnosis was entertained despite the infant's age. Lumbar tap showed xanthochromic fluid containing few crenated red cells, with a sugar level of 65 mg/100 cc. and a protein level of 71 mg/100 cc. Blood was drawn for calcium determination and the baby was given calcium chloride administered in the feeding formula. Thirty-six hours post partum the mother was found to be tremulous and perspiring, with a runny nose, these symptoms having been present for 12 hours at the time. Puncture marks were found on her arms, and she gave a history of heroin addiction of one year's duration, the last dose having been taken intravenously 48 hours prior to delivery. The infant's symptoms subsided slowly over the next five days without any further treatment. Serum calcium level in the sample taken before administration of calcium chloride was subsequently reported as 9.8 mg/100 cc. The infant had no feeding difficulty and thrived throughout the neonatal period.

Symptomatology

The clinical appearance of the baby with narcotic withdrawal symptoms is as follows: The infant has an annoying high-pitched continuous cry; he is extremely irritable, and he is hyperactive and very jittery. His Moro reflex is incomplete, and deep tendon reflexes are increased. In severe cases generalized convulsions occur and may be repeated; vomiting, anorexia, and weight loss may be striking. Symptoms persisted for five to six days in the untreated cases reported here. It is difficult to ascertain from previous reports the duration of symptomatology in treated cases.

Comment

Unlike that in Cases 1 and 2, the diagnosis in Case 3 was obscured by the initial absence of the history of drug addiction in the mother. Furthermore, owing to the administration of meperidine to the mother, withdrawal reactions were delayed in both mother and child. The diagnosis of hypocalcemic tetany was entertained at first in this case on the basis of suggestive clinical findings, namely, twitching of facial muscles and positive Chvostek, Trousseau, and peroneal signs.

It should be noted that on the basis of cases reported by Goodfriend et al.[3] and also of other infants observed in this hospital, withdrawal reactions do not occur in the newborn infant unless the mother has taken the drug consistently, the last dose being taken less than a week prior to birth of the child. The symptoms found in the present cases are similar to those reported in the literature as tabulated by these authors[3]; in particular, the continuous high-pitched cry and extreme restlessness were noted in nearly all published reports. The cry of these infants is particularly noteworthy; it is louder, higher-pitched, and more continuous than the cry ordinarily observed in infants with organic disturbances of the central nervous system.

The physiological basis for the existence of somatic drug dependence in the fetus and newborn was elucidated by Shute and Davis,[4] who showed that morphine readily passes the placental barrier and produces varying degrees of asphyxia in utero, as indicated by changes in the rate and rhythm of the fetal heart. However, these authors further found that individual susceptibility to drug effects varied widely for the same dosage.

Early authors, such as Pettey,[1] expressed the opinion that morphine is secreted in the milk and that continued administration of the drug to the mother would render the infant symptom-free. Terwilliger and Hatcher,[5] however, were unable to extract morphine from mother's milk even when

large doses of the drug were administered. As the exact chemical changes undergone by morphine and heroin in the body are not known,[1] and as, on the other hand, some reported patients improved on breast milk from nonaddicted wet-nurses,[2] the role of possible secretion of opiates in the milk is not clear at this time. In the cases reported here, none of the mothers nursed, and the infants became asymptomatic without treatment.

The mothers of all three infants had been taking heroin intravenously. They had had previous hospitalization for complications arising from this mode of administration, such as infectious hepatitis, localized cellulitis, and thrombophlebitis of the upper extremities. All had multiple puncture marks on the arms; a search should always be made for these even on the face of denial of drug addiction.

It should be noted that the finding of clinical manifestations of narcotic withdrawal in the newborn as described does not preclude the presence of other pathology which may account for some of the manifestations, for which a search should always be made.

Although the patients reported here improved without treatment, most authors recommend the administration of opiates and/or barbiturates. Goodfriend et al. used barbiturates in their cases. The fact that the patients reported here improved without treatment should not be considered necessarily a contradiction of the findings of these other authors, since treatment recommended by them may well be necessary when clinical manifestations are sufficiently severe.

Summary and Conclusions

Three cases of apparent heroin diacetylmorphine withdrawal reactions in the newborn are described.

The following findings characterize this syndrome: (1) in the mother: (*a*) history of heroin addiction, the last dose being taken less than a week prior to birth of the child; (*b*) presence of needle marks on the arms; (2) in the infant: (*a*) a characteristic high-pitched continuous piercing cry; (*b*) hyperirritability; (*c*) coarse tremors and twitching of extremities and facial muscles, which may approach a generalized convulsion in intensity.

In the infants reported here all abnormal findings disappeared without any specific treatment. No residual abnormalities were noted. However, the literature indicates that treatment by opiates and/or barbiturates is necessary in severer cases, and I do not believe that this recommendation is contradicted by my findings.

All the mothers had clinical heroin withdrawal reactions, but there was no evidence of a direct relationship between the severity of their reactions and those of the infants.

The importance of considering narcotic withdrawal reactions in the differential diagnosis of hyperirritable states of the newborn is again emphasized.

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REFERENCES

1. Pettey, G.: Memphis M. Month. *32*:57, 1912.

2. Menninger-Lerchenthal, E.: Monatsschr. Kinderh. *60*:182, 1934.

3. Goodfriend, M. J.; Shey, I. A., and Klein, M. D.: Am. J. Obst. & Gynec. *71*:29, 1956.

4. Shute, E., and David, M.: Surg. Gynec. & Obst. *57*:727, 1933.

5. Terwilliger, W. G., and Hatcher, R. A.: Surg. Gynec. & Obst. *58*:823, 1934.

Simultaneous Occurrence of Mongolism and Leukemia

Report of a Nationwide Survey

WILLIAM KRIVIT, M.D., and ROBERT A. GOOD, Ph.D., M.D., Minneapolis

The reports of the simultaneous occurrence of leukemia and Mongolism by Schunk (two cases),[1] Bernhard (three cases),[2] Krivit and Good (five cases),[3] and Merrit and Harris (four cases)[4] and the personal communications of Dr. Sydney Farber (eight cases) and Dr. James Wolff (four cases) prompted a nationwide survey to determine the incidence of this entity. The observation of a surprisingly large number of patients with concomitant leukemia and Mongolism was indeed intriguing and provoked an effort to determine whether or not the joint occurrence of these two diseases was fortuitous or biologically significant.

It was reasoned that if this surprising combination of unusual diseases were found to occur more frequently than could be explained by chance, a common denominator for the two disorders might be sought. For example, among the etiologic possibilities one might consider teratogenic forces (i. e., virus infection, nutritional factors, toxicity, or stress) occurring at a critical period in gestation which might result in both anomalies. On the other hand, the combined occurrence of Mongolism and leukemia might reflect the increased susceptibility of Mongoloid children to the induction of leukemia in the prenatal and postnatal period.

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From the Department of Pediatrics and the Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota. American Legion Memorial Heart Research Professor of Pediatrics. (Dr. Good).

To check the possibility that the joint occurrence of Mongolism and leukemia is more than coincidental, questionnaires were sent to more than 300 medical centers in the United States. In the questionnaire we simply asked whether or not the persons interrogated had observed the simultaneous occurrence of leukemia and Mongolism and requested details concerning cases recently observed. To conserve effort on the part of the reporting physician and consequently to gain cooperation for our study, we did not request data concerning the actual frequency of leukemia among the Mongoloid populations reported. We felt that should a great disproportion exist between the actual incidence of simultaneous leukemia and Mongolism and that expected by chance association it would be apparent from this type of survey, since reasonably accurate estimates of the incidence of the two diseases in the population at large are available. The results of this study permit the conclusion that leukemia and the Mongoloid constellation occur much more frequently than can be explained by chance alone and offer a provocative departure for future investigations into the nature of both diseases.

In Table 1 are recorded the number of questionnaires sent out, the number completed and returned, the number of cases of Mongolism occurring together with leukemia reported, and the total number of physicians or centers reporting cases. Although cer-

TABLE 1.—*Results of Survey*

	Number
Cases of Mongolism-leukemia syndrome reported	66
Physicians or centers reporting cases	31
Questionnaires sent out	300
Questionnaires returned	125

TABLE 2.—*Simultaneous Occurrence of Leukemia and Mongolism in the Zero- to Four-Year-Old Age Group During 1952 Through 1955, Inclusive*

Case	Responsible Reporter	Hospital	Author's Case No.	Birth Date	Age at Diagnosis of Leukemia	Type of Leukemia
1	Bigler, J. A.	Children's Hosp., Chicago		4/25/49	4 yr.	Stem-cell
2	Farber, S.	Children's Hosp., Boston		2/26/52	Newborn	Myelogenous
3	Farber, S.	Children's Hosp., Boston		1952	2 yr.	Myelogenous
4	Farber, S.	Children's Hosp., Boston		7/14/53	3 mo.	Myelogenous
5	Farber, S.	Children's Hosp., Boston		8/26/53	2 yr. 10 mo.	Myelogenous
6	Farber, S.	Children's Hosp., Boston		6/29/52	2 1/3 yr.	Acute leukemia: atypical leukemia
7	Galloway, E.	Conf. Mem. Hosp., Shreveport		6/11/49	4 yr.	Lymphatic
8	Harris, J.[a]	Duke Hosp., Durham	2	1948	4 yr.	Lymphatic
9	Harris, J.[a]	Duke Hosp., Durham	3	1950	3 yr.	Myelogenous
10	Harris, J.[a]	Duke Hosp., Durham	4	1953	2 yr.	Myelogenous
11	Kingberg, W.	Wash. Univ., St. Louis		9/13/53	14 mo.	Lymphatic
12	Authors[a]	Univ. of Minn.	1	1951	2 yr.	Myelogenous
13	Authors[a]	Univ. of Minn.	2	1952	2 yr.	Lymphatic
14	Authors[a]	Univ. of Minn.	3	1954	Newborn	Lymphatic
15	Authors[a]	Univ. of Minn.	4	1955	Newborn	Myelogenous
16	Authors[a]	Univ. of Minn.	5	1952	2 1/2 yr.	Lymphatic
17	Lyman	Iowa U., Iowa City		3/29/51	3 yr.	Lymphatic
18	Lyman, M.	Iowa U., Iowa City		1/14/53	2 yr.	Lymphatic
19	Lubey, M. E.	Cincinnati, Ohio		12/31/53	17 mo.	Myelogenous
20	Mills, D. S.	Mayo		12/10/51	4 yr.	Lymphatic
21	O'Connor, R. E.[a]	Kern Gen. Hosp., Calif.		1953	Newborn	Myelogenous
22	Schunk, G.	Oregon Univ.		1953	24 mo.	Lymphatic
23	Schunk, G.[a]	Oregon Univ.	1	7/16/52	Newborn	Myelogenous
24	Smith, N. J.	U.C.L.A.		1954	Newborn	Myelogenous
25	Thelander	U. Calif. Child.		4/15/50	4 yr.	Stem-cell
26	Taylor	Anderson Hosp.		1953	2 yr.	Lymphatic
27	Holman, A. N.	Harriet Lane Home		1951	3 1/2 yr.	Lymphatic
28	Water, W. J.	Syracuse		5/15/52	3 yr.	Stem-cell
29	Wolf, J. A.	Columbia	1	1952	Newborn	Stem-cell
30	Wolf, J. A.	Columbia	3	1951	22 mo.	Lymphatic
31	Wolf, J. A.	Columbia	4	1951	10 mo.	Lymphatic
32	Weisfuse, L.	Hempstead, N. Y.		1952	18 mo.	Lymphoid
33	Children's Memorial	Hospital, Omaha		7/12/52	19 mo.	Lymphatic
34	Borges, W.	Babies and Children, Cleveland		2/1/53	20 mo.	Lymphatic

[a] A. M. A. Am. J. Dis. Child. 88:740, 1954.

tain of the large medical centers reported multiple cases, no particular geographical distribution was observed from the reports; indeed, the combined disorder has been observed in all parts of the country. In Table 2 all cases of combined leukemia and Mongolism occurring between Jan. 1, 1952, and Dec. 31, 1955, in children 0 to 4 years of age are listed according to an alphabetical arrangement of the responsible reporting physician. This age group and these years were chosen for several reasons. First, the incidence of leukemia in this age group seems to be well established, and these data are available from the U. S. P. H. S. Bureau of Vital Statistics. Second, the incidence of Mongolism for this age group and this period may be estimated with reasonable accuracy. Further, the tendency of Mongoloid children to die at an early age might make observations on older children difficult to evaluate statistically.

As can be seen in the Table, 34 cases of combined Mongolism-leukemia syndrome were observed during this period among children 0 to 4 years of age. In all instances the leukemia was acute or subacute. Seventeen of the cases were designated as lymphatic, 12 as myelogenous, 4 as stem-cell, and 1 as atypical acute leukemia. Among the 34 patients, 7 had leukemia which was diagnosed in the neonatal period and which may be considered to have been congenital.

Of further interest was the observation that six cases of simultaneous leukemia and Mongolism were reported for the first half of 1956 alone. These cases are recorded in Table 3. It is indeed striking that three of these six cases were Mongoloid children with congenital leukemia.

Comment

In attempting to determine whether these results indicate that Mongolism and leukemia occur together more frequently than can be explained by chance association, the following questions were posed.

First, what is the estimated maximum number of children with Mongolism in the United States in the 0- to 4-year age range

TABLE 3.—*The Simultaneous Occurrence of Mongolism and Leukemia in 1956 in the Zero- to Five-Year-Old Age Group*

Case	Responsible Reporter	Hospital	Birth Date	Age at Diagnosis of Leukemia	Type of Leukemia
1	Andrea, J. F.	Dover, Ohio	1956	Newborn	--
2	Bergan, R. O.	Duluth Clinic, Duluth, Minn.	1954	May, 1956	Lymphatic
3	Des Forges, S. F.	Boston City Hospital	1956	Newborn	Myelogenous
4	Egbert, D. S.	Luther Hosp., Fort Dodge, Iowa	9/1/55	7 mo.	Lymphatic
5	Lee, C. H.	Driscoll Child. Hosp., Corpus Christi, Texas	2/16/56	Newborn	Lymphatic
6	Meiks, L. T.	Indiana Univ.	1951	5 yr.	--

each year? This figure would represent the number of Mongoloid children at risk to leukemia each year. Second, how many random occurrences of the two diseases would be anticipated if the incidence of leukemia among the Mongoloid children were the same as in general population?

As to the former, Beidelman [5] reported the highest incidence of Mongolism in 1000 live births as 3.4, or 1:294. However, Carter and MacCarthy [6] showed a frequency of 1:660 births in England. In our estimation of the Mongoloid population for purposes of this study, the most liberal estimate, 1:294, will be used. This choice of data then will provide a figure for the number of Mongoloid children at risk exceedingly in excess of that which would be obtained using the more conservative estimates of the frequency of birth of Mongoloid children. The further assumption that all Mongoloid children will live four years will be made. Obviously, because many Mongoloid children die from intercurrent infection during the first four years, this assumption will provide an estimation of Mongoloid children considerably larger than the true population at risk.

The total population in the 0- to 4-year age group is 17,472,000.[7] Granting the highest incidence of Mongoloid birth and the unlikely possibility that all Mongoloids live at least four years, there are 1/294× 17,472,000, or 59,400, Mongoloids in the 0- to 4-year age group for any one year. There must, therefore, be 237,600 mongol risk years for a four-year period (Table 4).

In answer to the second question, there are reported for the general population of the 0- to 4-year age group for 1952, 1953, and 1954 an average of 910 cases of leukemia per year, or, as stated otherwise, the incidence is 1:19,200 among infants and children 0 to 4 years of age for each year of risk.[8] From these figures one may estimate that, if chance alone were operating, 12.3 cases of combined leukemia and Mongolism would be expected to occur during this four-year period. Or, figured another way, if each year there are 910 cases of leukemia and the incidence of Mongolism is 1:300 in the population at large, chance association would result in the simultaneous occurrence of 3 cases of the two diseases per year and approximately 12 cases during the four-year period. However, Table 2 indicates that a minimum of 34 such cases were observed during the four-year period under consideration, or an incidence of joint expression of these diseases approximately three times that anticipated. This discrepancy between reported and anticipated cases is even more striking when several factors are considered. Obviously not all cases of this entity occurring during the 1952-1955

TABLE 4.—*Estimation of Mongol Population*

Year	General Population in 0- to 4-Yr. Age Group [a]
1952	17,153,000
1953	17,436,000
1954	17,827,000
Average/yr.	17,472,000
Mongols/yr.	59,400
(1:294 births, and assuming that all Mongoloids live 4 yr.)	
Mongol risk years for 1952, 1953, 1954, and 1955	237,600

TABLE 5.—*Incidence of Leukemia in the Zero- to Four-Year Age Group General Population*

Year	Cases of Leukemia, [a] No.
1952	935
1953	872
1954	922
Average/yr.	910
Incidence/yr. = 17,472,000 ÷ 1:19,200	
	910

TABLE 6.—*Theoretical Expectancy of Leukemia Occurring in Mongoloids by Coincidence*

	Number
Mongol risk years	237,600
Incidence of leukemia in general population	1:19,200
Expected number of Mongoloids with leukemia	12.3
Observed number of Mongoloids with leukemia	34

period have been reported to us. This conclusion is supported by the fact that numerous physicians with whom we have had personal contact have noted instances of the combination but have not contributed them to the survey. For this reason, and since not all Mongoloid children live four years and our "at risk" figures have purposely not taken into account the decreasing population of Mongoloid children, the 12.3 cases anticipated over the four-year period is an absolute maximum and the 34 observed cases reported represent an absolute minimum. Using these figures as the basis for statistical analyses,* the significance of this observation can be established. With the incidence of leukemia and Mongolism considered above, the likelihood of 34 cases of disease occurring by chance association during a four-year period would be less than once in 1000 times.

Of perhaps even greater significance are the number of cases of leukemia-Mongolism syndrome reported during the first half of 1956. The six cases observed in a six-month period amount to approximately half of the theoretical total of 12.2 cases anticipated to occur during an entire four-year period. Further, the observation of three cases of congenital leukemia during this six-month period is striking. Of the 2,000,000 infants born during this period, a maximum of 6800 would be Mongoloid infants (1:294 births). Three persons with congenital leukemia among these Mongoloid infants for this period would provide an incidence of 1 case of congenital leukemia per 2266 Mongoloid children, or nine times the rate of occurrence of all the leukemia which would be anticipated for the entire 0- to 4-year age group in the population at large (1:19,200).

These data seem to establish that a common factor is operating to result in the occurrence of leukemia in Mongoloid children in a frequency far in excess of its occurrence in the general population. A prospective study would be even more convincing. The finding of more than 20 such simultaneous occurrences of leukemia and Mongolism during 1956 and 1957 would be conclusive. Therefore, we earnestly urge all physicians who encounter a case of leukemia and Mongolism in children 0 to 4 years of age during 1956 or 1957 to report the case to us. The positive prospective demonstration that the simultaneous occurrence of these two rare diseases is more than circumstantial might be most important in the ultimate understanding of the nature of either or both diseases.

Summary

A nationwide survey revealed that in the years 1952-1955, inclusive, a minimum of 34 cases of simultaneous leukemia and Mongolism occurred in the United States in the 0- to 4-year age group.

The maximum number of cases of the combined disorder to be anticipated by chance alone is calculated to be 12.3 for the four-year period for the same age group in the population at large. Thus the actual occurrence of simultaneous leukemia and Mongolism during this period was approximately three times higher than that which might be anticipated to result from chance association. These differences are statistically significant.

Seven cases of Mongolism with congenital leukemia were reported to us as having been observed in 1952-1955.

Six patients with combined leukemia and Mongolism were reported during the first

* N=estimated number of mongol risk years; r=estimated yearly leukemia incidence rate; $E=Nr$=estimated expected number of leukemic Mongoloid children during the time interval; O=observed number of leukemic Mongoloids during the time interval; $K=\frac{O-E}{\sqrt{E}}=\frac{34-12.3}{\sqrt{12.3}}=6$; $P<0.001$

half of 1956. Three of these patients had congenital leukemia, an incidence of congenital leukemia among newborn Mongoloid children nine times higher than that of all leukemias in children 0 to 4 years of age.

A solicitation of reports of all cases of leukemia-Mongolism syndrome observed during 1956 and 1957 in children 0 to 4 years of age is made.

Dr. Eugene A. Johnson, Assistant Professor of the Division of Biostatistics gave assistance in calculating the statistical significance.

420 Heart Hospital, University of Minnesota (14) (Dr. Good).

REFERENCES

1. Schunk, G. J., and Lehman, W. L.: Mongolism and Congenital Leukemia, J. A. M. A. 155: 250-251, 1954.

2. Bernhard, W. G.; Gore, I., and Kilby, R. A.: Congenital Leukemia, Blood 6:990-1001, 1951.

3. Krivit, W., and Good, R. A.: The Simultaneous Occurrence of Leukemia and Mongolism: Report of 4 cases, A. M. A. J. Dis. Child. 91:218-222, 1956.

4. Merrit, D. H., and Harris, J. S.: Mongolism and Acute Leukemia: A Report of 4 Cases, A. M. A. J. Dis. Child. 92:41-44, 1956.

5. Beidelman, B.: Mongolism: A Selective Review, Am. J. Ment. Deficiency 50:35, 1945-1946.

6. Carter, C., and MacCarthy, D.: Incidence of Mongolism and Its Diagnosis in the Newborn, Brit. J. Soc. Med. 5:83-90, 1951.

7. Population by Age Group, in Vital Statistics of the United States, United States Department of Health, Education, and Welfare, 1952, 1953, and 1954, Vol. 1.

8. Death by Specific Disease According to Age, in Vital Statistics of the United States, United States Department of Health, Education, and Welfare, 1952, 1953, and 1954, Vol. 2, p. 64.

Use of Chlorpromazine in Two Hundred Seventy-Eight Mentally Deficient Patients

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The use of chlorpromazine* as a tranquillizer in the treatment of major psychiatric symptoms has frequently been reported.[1-12] Less information is available, however, on its use in controlling behavior disturbances in the mentally deficient patient.[13-17] Bonafede noted a reduction in irritability, hostility, and aggressiveness in 75 mental defectives with epilespsy who were given chlorpromazine. There was no reduction in the number of seizures.[13] Bair and Herold reported an improvement in I. Q., general behavior, and sleep patterns in 10 hyperactive retarded children given chlorpromazine.[14] Improved manageability of overactive and destructive patients was noted by Rettig, as well as a lessening of disciplinary and custodial duties of the hospital personnel.[15] Both MacColl and Horenstein have reported significant degrees of improvement in the behavior of treated patients.[16,17]

The purpose of this presentation is to report our experiences with chlorpromazine in treating behavioral symptoms in 278 mentally deficient patients.

Case Material and Methods

The patients were treated at Pacific State Hospital, a California institution for the mentally deficient. The hospital cares for all types and degrees of retardation and has an average daily population of 2700. The patients range in age from 1 year to 75, with the median around 20. Their intelligence quotients range from severely defective to borderline, with the median in the low 30's.

During the period of July 1, 1955, to July 31, 1956, a total of 320 patients received tranquillizing drugs. Of these, 278 were treated with chlorpromazine, 42 with reserpine, and 13 with promazine. Some were treated with a combination of drugs. This report is restricted to the results of chlorpromazine administration to 278 patients. The final assessment of results was carried out in October, 1956. The effects of reserpine and promazine paralleled those of chlorpromazine, which gained constantly in popularity and became the predominant tranquillizer. The drug was used in the hospital on the prescription of the attending physicians.

Table 1 shows the age and I. Q. distribution of patients who received chlorpromazine. A preponderance of severely retarded adolescent and adult patients is noted when compared with the age and I. Q. distribution of the general patient population. Fewer patients are noted within the youngest and oldest mildly retarded groups. The ratio of males to females was approximately equal, although in the general patient population it is 3:2.

Table 2 shows the average daily dose and range for each age group. The amount of medication was dependent upon the weight of the patient and therefore correlated with age. Chlorpromazine tablets were administered orally in divided daily doses. The tablets were split and crushed when

TABLE 1.—*Age and I. Q. of Patients Given Chlorpromazine*

I. Q.	Patients, No.				
	Age, Yr.				Totals
	1-9	10-19	20-29	30 and Over	
Under 20	15	52	30	11	108
20-49	21	28	42	26	117
50 and over	2	23	16	12	53
Totals	38	103	88	49	278

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*Chlorpromazine (Thorazine) from Smith, Kline & French Laboratories was used in the cases presented in this report.

TABLE 2.—*Daily Doses of Chlorpromazine, by Ages of Patients*

Age, Yr.	Daily Dose, Mg.	
	Av. (Mean)	Range
1–9	68	25–150
10–19	126	25–400
20–29	155	50–400
30 and over	162	50–700

necessary. A liquid form of chlorpromazine,† 30 mg. per cubic centimeter, was also tried, with each dose diluted in milk, fruit juice, or jam. Though this form of administration would seem desirable for small children, many resisted it because of a bitter taste, and its use was discontinued.

The effects of the drug were evaluated by the 13 attending physicians, who relied partly on the reports of the nursing personnel. The results were judged on a four-point scale by the degree of change in the specific symptom or symptoms for which the drug was prescribed. When the symptom no longer interfered with the patient's adaptation to his environment a score of 2+ was assigned, and 1+ was used when the symptom improved to such an extent that alterations toward the better could be made, either in the patient's general care or in some special aspect of his therapeutic program. The treatment was considered a failure when there was no change in the manifestations (0) or when an aggravation of the specific symptom was noted (−1).

Results

Table 3 relates the results to the ages of the patients, and Table 4 to the severity of retardation. Neither age nor the degree of retardation influenced the results significantly. Systematic psychological retesting was not done, but there was no clinical evidence that the medication in itself substantially or consistently improved the functioning mentality level of the patients.

† Thorazine Concentrate; Smith, Kline & French Laboratories.

TABLE 3.—*Response to Chlorpromazine, by Age Groups*

Age, Yr.	Patients, No.	Per Cent of Patients Showing Change			
		−1	0	1+	2+
1–9	38	0	18	42	40
10–19	103	6	25	39	30
20–29	88	9	10	42	39
30 and over	49	8	10	47	35

TABLE 4.—*Response to Chlorpromazine, by I. Q.*

I. Q.	Patients, No.	Per Cent of Patients Showing Change			
		−1	0	1+	2+
1–19	108	0	20	37	43
20–49	117	10	13	45	32
50 and over	53	11	17	45	27

Table 5 relates improvement to the length of treatment, which varied from 2 to 296 days. Of the 278 patients, 198, or 71%, were still receiving medication on July 31, 1956. There was a positive relationship between duration of treatment and good results because of the general tendency to continue medication for a patient showing a good response. Lack of improvement was the commonest reason for discontinuing treatment. There is no justification for prolonged use of the drug in the face of adverse or unsuccessful results.

TABLE 5.—*Response to Chlorpromazine, by Duration of Treatment*

Length of Treatment, Days	Patients, No.	Per Cent of Patients Showing Change			
		−1	0	1+	2+
0–60 *	115	8	26	38	28
61–120	107	4	13	50	33
121 and up	56	7	5	34	54

* This group includes both those patients who were not benefited by chlorpromazine and those whose acute symptoms were rapidly relieved by the drug.

Table 6 relates improvement to primary and secondary diagnoses; neither influenced results. All patients had a primary diagnosis of mental deficiency, but they represented a variety of etiological and symptomatic subclassifications. For the purposes of this presentation they were divided into two diagnostic groups. The mental deficiencies with easily demonstrable organic involvements of the brain were represented by 122

TABLE 6.—*Response to Chlorpromazine, by Diagnosis*

Diagnosis	Patients, No.	Per Cent of Patients Showing Change			
		−1	0	1+	2+
Organic	122	3	18	38	41
Nonorganic	156	8	16	44	32
With epilepsy	82	6	23	37	34
With psychosis	64	12	16	47	25

patients. The nonorganic group included the diagnostic subclassifications of familial, undifferentiated, and psychogenic types. There were 156 patients in this latter group. A slight preponderance of nonorganic patients is noted, probably because superimposed emotional problems were commoner in this group. Included in the latter classification are 21 young mentally deficient patients whose clinical symptoms indicated significant emotional problems and who were part of an intensive psychiatric therapy program. There were 82 cases who had clinical epilepsy in addition to the primary diagnosis and 64 in whom a superimposed psychosis was diagnosed prior to the administration of chlorpromazine. The frequency of both conditions, particularly that of psychosis, was much higher than is generally found among institutionalized mental defectives and indicates that chlorpromazine was frequently used for intercurrent psychoses and for personality disturbances.

The degree of improvement related to specific indications for chlorpromazine is listed in Table 7. General hyperactivity and

TABLE 7.—*Response to Chlorpromazine, by Indications*

Indication	Patients, No.	Per Cent of Patients Showing Change			
		−1	0	1+	2+
Hyperactivity	217	6	14	45	35
Aggressiveness	143	4	11	45	40
Withdrawal	52	8	12	40	40
Property-destructiveness	50	14	14	38	34
Self-injuriousness	48	6	27	32	26
To replace seclusion or restraint	36	17	19	36	28
Emesis and/or feeding problems	14	0	14	14	72
Others	8	12	76	12	0

aggressiveness against the self or the environment were the commonest indications. In many of the patients there was more than one indication. In 13 cases the drug was used to make the patient more accessible to psychotherapy, and these are included in the group designated "Withdrawal."

When improvement was measured by change in the specific symptom for which the drug was prescribed, about 70% to 80% of the patients showed benefits. There were 20% to 30% who remained unchanged, with aggravation noted in an occasional symptom. Early during the study the drug was tried with the hope it might improve some manifestations of epilepsy,[13,18,19] and occasionally it was used for such indications as noisiness at night and disturbing delusions. Success in these patients was very limited.

Complications

There were 27 instances of complications. They were all of a transitory nature, and 10 of the patients were continued on medication after an adjustment of the dosage. The commonest complication was drowsiness or lethargy in 14 cases. In 12 a rapid and significant increase in epileptic seizures occurred.[13,18,19] In 10 of these the initiation of chlorpromazine coincided with a decrease or discontinuance of phenobarbital medication. One patient consistently regurgitated the drug. An occasional contact dermatitis was noted in employees handling the liquid or crushed medicine.

Report of Cases

Four brief summaries are presented to demonstrate our experiences.

CASE 1.—A 12-year-old boy had mental deficiency which had been noted in early childhood. It was manifested by general retardation and was complicated by severe behavioral problems. He constantly disrobed himself, masturbated publicly, and ran away at every opportunity.

He was admitted to the hospital at the age of 6½ years. His adjustment was poor. He functioned at an I. Q. level of 38 and refused to eat or drink until his food was first tasted. He showed a fear of doorways and was preoccupied with shadows. He was mute, hyperactive, and explosive. He developed no interpersonal relationships. The diagnosis was mental deficiency, undifferentiated, probably due to psychogenic causes.

He improved slowly, developing some speech, which was echolalic, volatile, and explosive. A daily dose of 100 mg. of chlorpromazine was started. Shortly thereafter he began to relate to the nursing personnel, started to feed himself, and helped with the feeding of more helpless patients. At present he dresses himself, keeps his clothes on, and is able to talk in good sentences. After initial improvement with chlorpromazine, play therapy was also started.

CASE 2.—The patient was an 11-year-old boy in whom mental deficiency was noted early. He was an extreme behavior problem; he made several sexual attempts on his younger sister. He was admitted to the hospital at the age of 8½ years because of his aggressive hyperactivity.

His adjustment in the hospital was no better. He attacked other patients, burned them with hot dishes removed from the dishwashing machine, crawled into closets, and showed strikingly bizarre behavior. On psychological tests he functioned at an I. Q. level of 70. The diagnosis was mental deficiency, undifferentiated, probably due to psychogenic causes.

Chlorpromazine was started in a daily dose of 100 mg. A dramatic change occurred in his behavior. While previously it was described as "impossible," shortly thereafter the nurses' notes stated, "change of behavior astonishing." He became cooperative, pleasant, and mannerly; tried hard to do the proper things; helped with the care of younger patients; spoke in friendly fashion, and made every attempt to be pleasing. The administration of chlorpromazine was followed two months later by the initiation of individual psychotherapy.

CASE 3.—The patient was a 28-year-old man in whom signs of mental deficiency were noted following an attack of encephalitis at the age of 2½ years. He became hyperactive and had repeated severe outbursts of aggressiveness. He was admitted to the hospital at the age of 15 years.

His hospital adjustment was poor. He remained hyperactive and became self-destructive, chewing at his shoulders, at times causing severe injury to himself. Physical restraint was often necessary. His I. Q. was 10. The diagnosis was mental deficiency, postinfectious. He was given 400 mg. of chlorpromazine daily. Marked improvement was noted; no restraint was necessary, and his self-destructive behavior ceased. He gained weight and appeared physically healthier in all respects.

CASE 4.—The patient was a 23-year-old man in whom mental deficiency was first evidenced at the age of 4 because of delayed speech, which was indistinct and mostly incoherent. He had a tendency to wander away from home and was unaware of dangers; he was frequently picked up wandering aimlessly in the middle of a street. He was destructive and cruel to other children. For these reasons he was admitted to the hospital at the age of 9 years.

In the hospital he remained a severe management problem. He was hyperactive, aggressive, and destructive, breaking windows and attacking other patients almost constantly. His I. Q. was 21. The diagnosis was mental deficiency, undifferentiated. A daily dose of 300 mg. of chlorpromazine was started, and his behavior improved. He ceased to be hyperactive and aggressive and became cooperative, at times even polite.

Comment

The material presented describes our clinical experiences with chlorpromazine in a large hospital for the mentally retarded. It does not represent the results of a preplanned research project. The drug was not administered by a blind technique, and the results were judged by the observations of attending physicians and nursing personnel. Each patient served as his own control.

There were many possible biases. The patients who were selected for treatment from the large hospital population probably included those whose symptoms were least tolerable to the nursing personnel or the attending physicians. It is likely, therefore, that any sign of improvement was so enthusiastically received by the observers that evaluations became biased toward the positive. The selection of a patient for treatment, the administration of the drug, and the observations made after drug therapy could have, in themselves, significantly altered the relationship between a patient and his environment and relationships to other persons. The patient previously considered intolerable was now regarded with optimism because of improved interpersonal relationships, and this factor probably acted synergetically with the drug to effect an improvement.

Only a double blind technique could have avoided many of these biases. Such procedure should have made comparisons between an experimental and a control group possible. Even with double blind technique, however, many problems would have remained unsolved in the evaluation of a drug like chlorpromazine, which produces physiological changes during administration. This difficulty was clearly noted during another study conducted by members of the hospital staff on the use of chlorpromazine as a preoperative medication in poor-risk or uncooperative patients. The results were encouraging and will be reported elsewhere.[20]

It was noted during this experiment that the observers could easily identify the patients receiving chlorpromazine by their perioral pallor.

A most important conclusion from our study concerns the need for developing valid measurements for deviant human behavior. Many investigators have attempted this in the past. Their work was usually part of an evaluation of a specific therapeutic agent or technique. Some authors believe their particular adjustment scale valid for work with a given hypothesis, but as yet no generally adequate yardstick has been developed for the measurement of behavior. If such a device were available, future work would be greatly simplified.

We believe, however, that limited conclusions can be drawn from our work. The drug was administered on several wards, and the observations came from numerous attending physicians and groups of nursing personnel. Their findings concerning the efficacy of the drug did not vary greatly. It is likely, therefore, that no bias was introduced by any single observer and that there was a reasonable degree of consistency in observations.

Our findings show that chlorpromazine can be administered with reasonable safety under careful observation. An increase in frequency of epileptic seizures was the most significant complication. When chlorpromazine is administered to patients with known epilepsy, or known cerebral dysrhythmia, the anticonvulsant medication should be carefully scrutinized and adjusted. Under no circumstances should chlorpromazine be considered a substitute for an anticonvulsant. In some cases the introduction of chlorpromazine should parallel an increase in anticonvulsants such as diphenylhydantoin sodium. With these precautions chlorpromazine can be effectively and safely given to epileptics.

Drowsiness was another frequent complication in our series. A decrease in dosage usually eliminated this side-effect. The concurrent administration of stimulants may occasionally be necessary. We found no instances of such complications as jaundice, Parkinsonism, skin rash, or blood dyscrasia, as reported by others.[1,2,3]

Chlorpromazine appeared effective in the amelioration of such symptoms as hyperactivity, aggressiveness, and withdrawal and assisted in the establishment of psychotherapeutic relationships in some patients when such symptoms seriously interfered with the therapeutic procedure. The drug, in itself, did not prove to be of curative value; nor was it considered a therapeutic agent to be used singly or as a replacement for other psychiatric techniques. It could not substitute for activity programs, wholesome environmental contacts, training, or schooling, and it did not eliminate the need for psychotherapy. Its tranquilizing effects, however, made patients more accessible and made the initiation of appropriate programs easier.

Chlorpromazine, in itself, did not increase intelligence, as reported by others.[14] Where hyperactivity or withdrawal, however, interfered with the testing process, at times its administration, through beneficial effects on secondary symptoms, substantially improved the numerical score obtained on intelligence tests.

From our observations with disturbed mental defectives it appears likely that chlorpromazine may be successfully used in the psychiatric treatment of acutely disturbed or psychotic children. Since most serious psychiatric symptoms are of a chronic nature in children, and since there is a tendency to continue the drug in successful cases, care should be exercised not to use chlorpromazine on a prolonged basis in young patients until more is known about the long-range effect of the drug on the learning ability and attention span of children. Our present lack of knowledge concerning these facts should be a warning against the indiscriminate use of tranquilizing drugs in children, and an attempt to withdraw or decrease the drug should be

made as soon as beneficial effects seem stabilized.

Most mentally retarded children are institutionalized because the home environment is no longer capable of caring for them. Hyperactivity, aggressiveness, withdrawal, and feeding difficulties are the commonest specific symptoms that precipitate institutionalization. Chlorpromazine, in a substantial number of cases, helps in the management of these symptoms. It is suggested that physicians may utilize this drug for the treatment of the hyperactive or withdrawn mentally deficient patients. Institutionalization, which may be indicated because of undesirable behavior, may thereby be avoided in some cases.

Summary

Chlorpromazine in doses ranging from 25 to 700 mg. per day was administered to 278 mentally deficient patients.

The drug was considered by attending physicians to be an efficient and worth-while medication for such symptoms as hyperactivity, aggressiveness, and withdrawal.

Subjective evaluation demonstrated the efficacy of the drug for these symptoms in 70% of the cases.

The drug is not a substitute for a wholesome environment. It can, however, help in the initiation of many psychotherapeutic programs.

Drowsiness and a tendency toward increased seizures in epileptics were the commonest complications and were observed in 10% of the patients.

Chlorpromazine could be of substantial help in the home care of the hyperactive or withdrawn mentally retarded patient.

Before chlorpromazine or other tranquilizing drugs are prescribed for young patients, there is a need for investigating their effects on the intellectual and emotional growth of the average child.

The medical and nursing personnel of Pacific State Hospital helped in this study.

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REFERENCES

1. Chlorpromazine and Mental Health: Proceedings of the Symposium Held Under the Auspices of Smith, Kline and French Laboratories, June 6, 1955, Philadelphia, Lea & Febiger, 1955.

2. Psychopharmacology: A Symposium Organized by the Section on Medical Sciences of the American Association for the Advancement of Science and the American Psychiatric Association, and Presented at the Berkeley Meeting, Dec. 30, 1954, edited by N. S. Kline, Publication 42, Washington, D. C., American Association for the Advancement of Science, 1956.

3. Freeman, H.: A Critique of the Tranquilizing Drugs, Chlorpromazine and Reserpine, in Neuropsychiatry, New England J. Med. 255:877 (Nov.) 1956.

4. Freeman, H.; Arnold, A. L., and Cline, H. S.: Effects of Chlorpromazine and Reserpine in Chronic Schizophrenic Patients, Dis. Nerv. System 17:213 (July) 1956.

5. Feldman, P. E.; Lacy, B. S.; Walker, A. E., and Garvez, N. J.: Controlled Blind Study of Effects of Thorazine on Psychotic Behavior, Bull. Menninger Clin. 20:25 (Jan.) 1956.

6. Rinaldi, F.; Rudy, L. H., and Himwich, H. E.: Clinical Evaluation of Azacyclonal, Chlorpromazine, and Reserpine on Group of Chronic Psychotic Patients, Am. J. Psychiat. 112:678 (March) 1956.

7. Zeller, W. W.; Graffagnino, P. N.; Cullen, C. F., and Reitman, H. J.: Use of Chlorpromazine and Reserpine in Treatment of Emotional Disorders, J. A. M. A. 160:179 (Jan.) 1956.

8. Kielholz, P., and Labhardt, F.: Treatment of Mental Disorders with Chlorpromazine, J. Clin. & Exper. Psychopath. 17:38 (Jan.) 1956.

9. Tenenblatt, S. S., and Spagno, A.: Controlled Study of Chlorpromazine Therapy in Chronic Psychotic Patients, J. Clin. & Exper. Psychopath. 17:81 (Jan.) 1956.

10. Fromm, G. H., and Forsberg, I. A.: Controlled Study on the Value of Chlorpromazine in Allaying Anxiety, Dis. Nerv. System 17:16 (Jan.) 1956.

11. Kovitz, B.; Carter, J. T., and Addison, W. P.: A Comparison of Chlorpromazine and Reserpine in Chronic Psychosis, A. M. A. Arch. Neurol. & Psychiat. 74:467 (Nov.) 1955.

12. Kinross-Wright, V.: Chlorpromazine: Major Advance in Psychiatric Treatment, Postgrad. Med. 16:297 (Oct.) 1954.

13. Bonafede, V. I.: Chlorpromazine (Thorazine) Treatment of Disturbed Epileptic Patients:

Preliminary Report, A. M. A. Arch. Neurol. & Psychiat. 74:158 (Aug.) 1955.

14. Bair, H. V., and Herold, W.: Efficacy of Chlorpromazine in Hyperactive Mentally Retarded Children, A. M. A. Arch. Neurol. & Psychiat. 74: 363 (Oct.) 1955.

15. Rettig, J. H.: Chlorpromazine for the Control of Psychomotor Excitement in the Mentally Deficient: A Preliminary Study, J. Nerv. & Ment. Dis. 122:190 (Aug.) 1955.

16. MacColl, K.: Chlorpromazine Hydrochloride (Largactil) in the Treatment of the Disturbed Mental Defective, Am. J. Ment. Deficiency 61:378 (Oct.) 1956.

17. Horenstein, S.: Reserpine and Chlorpromazine in Hyperactive Mental Defectives, Am. J. Ment. Deficiency 61:525 (Jan.) 1957.

18. Meszaros, A. F., and O'Reilly, P. O.: Relation of Chlorpromazine to Epilepsy, Dis. Nerv. System 17:159 (May) 1956.

19. Schlichter, W.; Bristow, M. E.; Schultz, S., and Henderson, A. L.: Seizures Occurring During Intensive Chlorpromazine Therapy, Canad. M. A. J. 74:364 (March) 1956.

20. Jackson, T. L.; Carson, J. M., and Tarjan, G.: Pre-Operative Chlorpromazine in Poor-Risk and Uncooperative Mentally Deficient Patients Requiring Minor Surgical or Dental Care, to be published.

Progress in Pediatrics

Hypocalcemic States in Infancy and Childhood

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Hypocalcemia may manifest itself by a variety of seemingly unrelated signs and symptoms as well as by classical tetany. A low serum calcium may also be associated with diseases of several different bodily systems. During the past three years, 20 infants and children with hypocalcemia of varying etiology have been studied.

It is the purpose of this report to present a concise, orderly approach to the differential diagnosis of the low-calcium state. Clinical examples will be described in order to illustrate the conditions that may be associated with low levels of serum calcium. Diagnostic features, useful laboratory procedures, and methods of therapy will be discussed.

In any consideration of the possible causes of hypocalcemia, one must take into account the factors which affect calcium homeostasis. Figure 1 presents diagrammatically some of these factors, including those dependent upon dietary intake, those associated with metabolism of bone, those involved in excretory processes, and endocrine influences. It is also important to reemphasize the fact that the total serum calcium is composed of two chief components *: (*a*) a portion held in solution by virtue of being bound to serum proteins, this amount being proportional to the total concentration of proteins, and (*b*) a component present in the form of soluble calcium complexes. Although it is the total serum calcium which is ordinarily measured in the laboratory, it is the latter moiety which is ionized, freely diffusible in body fluids, and physiologically active. In reality, it is a decrease in serum ionizable calcium which causes clinical symptomatology. For purposes of this discussion, however, decreases of both total and of ionizable calcium have been grouped together.

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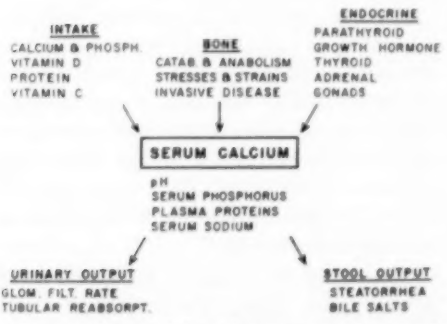

Fig. 1.—Factors influencing serum calcium level.

Etiology of Hypocalcemia

Utilizing the above framework, one can formulate a table of clinical causes of hypocalcemia (Table 1).

A. Defects in Intake.—Primary dietary deficiency of calcium, although common in certain Asiatic countries,[1] is of such rarity in the United States as to be of little clinical significance.

Although no longer a common cause of hypocalcemia, vitamin D-deficiency rickets occasionally may be associated with tetany. This is especially true during the healing phase of the disease.[2] The exact reasons for

* A third component consists of a small portion of the total serum calcium in the form of diffusible but not ionizable salts (citrate). This component is clinically unimportant.

TABLE 1.—*Etiology of Hypocalcemia*: Classification*

A.	Defects in intake
	1. Dietary deficiency of calcium
	2. Vitamin D-deficiency rickets
	3. Ingestion of oxalates, citrates, etc.
	4. Postacidotic tetany
	5. Hypertonic dehydration
	6. Hypoproteinemia
B.	Defects in absorption
	1. Congenital gastrointestinal malformation
	2. Fibrocystic and celiac disease
	3. Hepatic disease
	4. Acute pancreatitis
C.	Defects in urinary excretion
	1. Chronic nephritis
	2. Tubular disease
D.	Parathyroid disease
	1. Temporary insufficiency (tetany of newborn)†
	2. Postoperative tetany
	3. Idiopathic
	4. Pseudohypoparathyroidism‡
E.	Unclassified
	1. Neonatal hypocalcemia†
	2. Alkalosis
	3. Unknown

* Hypocalcemia refers to decrease of either total or ionized calcium concentration, the latter in certain instances existing without the former.

† It is not certain at this time whether or not Groups D1 and E1 are identical. Both should perhaps be cross classified under Category C.

‡ Pseudohypoparathyroidism may in reality be included in Category C.

this phenomenon are not well understood; several theories, including increased avidity of the bones for calcium and direct vitamin D-parathyroid antagonism,[3] have been suggested.

The following report of twins illustrates the association of tetany with rickets.

CASES 1 and 2.—The smaller of twin boys was admitted at the age of 3 months because of generalized convulsions occurring 20 minutes after he received the first diphtheria-pertussis-tetanus (D-P-T) injection. The brother was admitted that night, approximately eight hours after receiving a D-P-T injection, with similar symptoms. The spinal fluid of each infant was normal, but serum calcium concentrations were 5.8 mg/100 ml. and 6.6 mg/100 ml., respectively. Similar concentrations were found on three subsequent days, confirming the presence of hypocalcemia. In addition, serum alkaline phosphatase concentrations determined on many occasions varied between 40 and 87.5 K. A. units/100 ml. Roentgenograms demonstrated generalized demineralization of the bones, slight cupping at the distal ends of the radii, and thin sheaths of periosteal "new bone" deposited along the shafts of the tibiae, humeri, and ulnae. The x-ray picture was interpreted as being consistent with the healing stage of rickets. Careful questioning of the mother subsequently revealed that vitamin supplements had been started only two weeks prior to the occurrence of the convulsions.

Comment: No other cause of hypocalcemia was found, either at the time of hospitalization or during the subsequent 18-month follow-up period. It is presumed, therefore, that these twins exhibited generalized convulsions due to hypocalcemia associated with rickets. Although the administration of the D-P-T antigens obviously "triggered" the seizures, the exact mechanisms involved are obscure.

Ingestion of several chemical substances, such as oxalates and citrates, may cause tetany by their combining with ionized calcium in the serum, thereby forming insoluble complexes. The administration of large amounts of citrate during the course of blood transfusions, especially during exchange transfusions performed for treatment of erythroblastosis fetalis, although not causing gross hypocalcemia, may, nevertheless, cause clinical tetany.[4,5] For this reason, intravenous infusion of calcium has become routine during the exchange-transfusion procedure.

Two hypocalcemic syndromes associated with electrolyte disturbances induced by dehydration, especially in infancy, have been reported. Fortunately, the first, so-called "postacidotic tetany," is now rare. It was described in 1947 by Rapoport and coworkers[6] and occurred during the phase of recovery from the acidosis of infantile diarrhea. It is now the consensus of workers in the field that the form of tetany was related to the administration of large quantities of sodium lactate. Newer methods of parenteral fluid therapy employing smaller amounts of alkali have virtually eliminated this type of hypocalcemia.

The second syndrome is the form of hypocalcemia associated with hypertonic dehydration.[7,8] In this type of dehydration, children usually suffering from diarrhea show hypernatremia or hyperosmolarity of the serum. For some poorly understood reason, a low serum calcium level appears to be directly correlated with the height of the serum sodium.

Finally, in the category of disorders of intake, a low serum calcium level may be dependent upon a low level of proteins in

the serum. This may be found in starvation states as well as in other conditions associated with hypoproteinemia, such as nephrosis. Hypocalcemia of this nature rarely causes clinical symptoms, since the physiologically active ionized calcium remains normal or nearly so.

B. Defects in Absorption.—It is well known that defects in gastrointestinal absorption which lead to steatorrhea may be associated with hypocalcemia and tetany.[9] A combination of two mechanisms has been offered as an explanation for this phenomenon: (1) unabsorbed fatty acids form insoluble calcium "soaps" in the intestine, thus preventing absorption of calcium from the intestine, and (2) vitamin D, being fat-soluble, is dissolved in the unabsorbed fat and is excreted in the stool; a relative vitamin D deficiency thus results. Thus, in pediatric practice, conditions such as congenital malformations of the gastrointestinal tract, cystic fibrosis of the pancreas, and hepatic disease may interfere with fat absorption to such an extent as to produce hypocalcemia. The following cases are examples of hypocalcemia caused by defective absorption from the intestines.

CASE 3.†—A 2120 gm. premature girl manifested signs of intestinal obstruction, i. e., bile-stained vomitus and abdominal distention, during the second 24 hours of life. At operation, atresia of the upper jejunum was found and jejunal-ileal anastomosis was performed. After operation the infant was readmitted on two occasions for recurrence of vomiting and dehydration. During the second readmission generalized convulsions occurred after rehydration had been effected. Laryngeal stridor and a positive Chvostek sign were present. Figure 2 depicts the laboratory data, course, and therapy employed in this case.

Comment: It was postulated that the jejunal bypass was responsible for faulty gastrointestinal absorption with consequent production of steatorrhea and hypocalcemia. Confirmatory evidence was the presence of a low serum phosphorus concentration, indicating coexisting defective absorption of phosphorus. Low to low-normal levels of vitamin A, 27γ and 18γ/100 ml., were also obtained, lending support to the suggestion of difficulties with fat absorption.

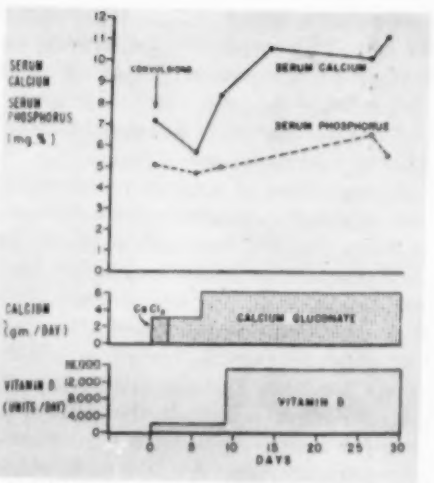

Fig. 2 (Case 3).—Laboratory data, therapy, and course of a 2½-month-old girl with hypocalcemia secondary to intestinal resection.

CASE 4.—A 5-week-old Negro girl was admitted because of cough and dyspnea. In addition to evidences of acute bronchiolitis, the infant was noted to have icteric sclerae, hepatomegaly, and dark urine. Laboratory studies were compatible with obstructive liver disease, i. e., presence of bile in the urine, with reduced quantity of urinary urobilinogen; absence of stercobilin in the stools; elevated total serum bilirubin of 8.8 mg/100 ml., with the direct-reacting fraction being 5.0 mg/100 ml.; elevated alkaline phosphatase of 55 K. A. units/100 ml., and normal flocculation tests. In order to exclude the diagnosis of nonsurgical obstructive jaundice ("inspissated bile syndrome"‡), a regimen of dehydrocholic acid (Decholin) intravenously and Ketochol"§ orally was instituted for three weeks. At the end of this period, improvement in both clinical icterus and most of the laboratory findings occurred. Elevation of the alkaline phosphatase concentration continued, however, and a low serum calcium level of 7.2 mg/100 ml. was noted. Three months after onset, "cupping" and "fraying" at the distal ends of the tibiae were demonstrated roentgenologically. Treatment with 4 gm. calcium lactate and 10,000 units of water-soluble vitamin D effected a gradual return of the calcium to normal and disappearance of the radiologic rachitic signs.

† Dr. Ralph E. Moloshok gave permission to include this patient.

‡ It is thought by many that this syndrome is in reality a form of infectious hepatitis.

§ Ketochol is a combination of the oxidized form of four bile acids (Searle & Co.).

Comment: Temporary interference with the entry of bile salts into the intestine was believed to have caused a decrease in fat absorption, with the consequent production of hypocalcemia and, in this instance, rickets without tetany.

Another form of hypocalcemia associated with a defect in gastrointestinal absorption is that caused by acute pancreatitis.[11] This condition is rare in children, but in adults the finding of a low total serum calcium concentration has been reported to be almost as useful a diagnostic index as elevated serum amylase. The postulated mechanism for this effect is that in the area of fat necrosis which results from the escape of pancreatic enzymes calcium is mobilized for the formation of "calcium soaps."

C. Defects in Urinary Excretion.—Two disturbances of renal function may lead to hypocalcemia. Firstly, a diminished glomerular filtration rate, regardless of etiology, will eventually cause retention of phosphorus in the body fluids.[12] A rise in serum inorganic phosphate concentration depresses total serum calcium as well as the ionized fraction. The reasons for this effect are poorly understood at the present time. Secondly, in primary renal tubular disease there is interference with the excretion of acid metabolites from the body. Instead, calcium stores are mobilized for this purpose and hypocalcemia may result (details later).

The following case is an example of hypocalcemia of renal origin.

CASE 5.—A 3-year-old boy had had classical nephrosis of childhood since the age of 17 months. At the onset of his disease he was treated with corticotropin and appeared to have a good diuretic response. Soon after, however, he began to exhibit signs of chronic renal dysfunction, i. e., persistent elevation of blood urea nitrogen levels and increased blood pressure values. A second admission was prompted by reaccumulation of edema which did not respond to corticotropin therapy. During the third admission a reduced urea clearance was recorded. At 32 months of age he was readmitted to the hospital for the fourth time because of tremulousness and five generalized convulsions which had occurred over the preceding five-week period. Figure 3 demonstrates the elevated serum

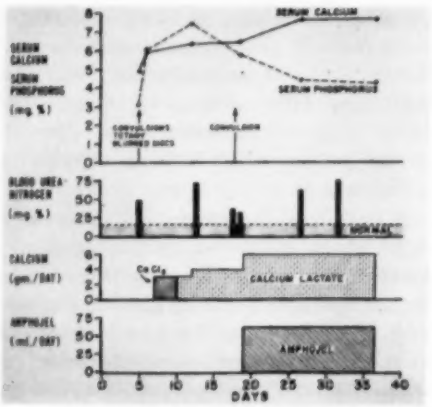

Fig. 3 (Case 5).—Laboratory data, therapy, and course of a 2¼-year-old boy with hypocalcemia secondary to chronic nephritis.

phosphorus and BUN levels and the hypocalcemia which were found on this admission. Also shown is the gradual return of serum calcium and phosphorus to normal as a result of administration of calcium salts and aluminum hydroxide. Although the child was maintained in relatively good electrolyte balance after this, he died eight months later of myocardial failure with intractable pulmonary edema.

Comment: It was felt that this patient's convulsions were due to hypocalcemia. Confirmatory evidence for this belief included the observation of episodes of typical tetanic twitchings, a positive Chvostek sign and blurring of the optic discs. The latter has been shown to be a concomitant of hypocalcemia, although its exact pathologic cause is not understood. Subsequent roentgenographic examination of the long bones demonstrated generalized demineralization and blurring of the metaphyseal ends of the shafts, other evidences of hypocalcemia. An electroencephalogram was not compatible with idiopathic epilepsy, and the hypertension never reached a height sufficient to be considered as a cause of the convulsions.

Some patients with primary renal tubular defects have lost the ability to produce an acid urine and to form ammonia. Both of these mechanisms are essential for the excretion of acid metabolites from the body. When these functions are defective, large quantities of fixed bases are mobilized for

excretion of acid radicals. Since calcium is the principal fixed base, existence of this defect will lead to continued loss of calcium in the urine, resulting in a tendency toward hypocalcemia. Clinically, described under many names[13-17] (Butler-Albright syndrome, Lightwood syndrome, base-losing nephritis, renal tubular acidosis), this syndrome occurs chiefly in babies under one year of age, although older children and adults have had the disease or its variants. The symptomatology in infants is characterized by loss of appetite with failure to thrive, constipation, apathy or irritability, and, frequently, thirst and polyuria. From the laboratory point of view, these children usually have a metabolic acidosis with lowered carbon dioxide-combining power and elevated serum chloride concentration, normal BUN, and a tendency to a decrease in ionized as well as total serum calcium. In the majority of cases the urine is alkaline and of low fixed specific gravity. Diagnosis can be confirmed by administration of a "provocative chloride load," as described by Crawford.[17] After a 24-hour control urine specimen is obtained, the patient is given 6 gm. of ammonium chloride per square meter per day for three days. At the end of this period, a second 24-hour urine specimen is collected. If the ammonium increment in the second urine specimen is not equal to 75% or more of the chloride increment, renal tubular acidosis may be suspected. Further evidence can be obtained by measuring the increase in titratable acidity and in sodium, potassium, and calcium excretion in the second specimen.

Therapy in this syndrome is directed toward relieving the acidosis and conserving the fixed base of the body. This is accomplished by administration of a mixture of sodium citrate (10 gm.) and citric acid (6 gm.) in 100 ml. of water. Although the underlying tubular defect is usually permanent, clinical improvement is most dramatic and gratifying.

D. Parathyroid Disease.—Possibly the chief determinant of calcium homeostasis in the body is the hormone or hormones (?) of the parathyroids. At least two specific effects have been ascribed to the secretions of these glands: (1) increased urinary phosphorus excretion, with consequent lowering of the serum phosphorus, owing to a specific inhibiting affect of parathyroid hormone upon reabsorption of phosphorus by the tubules; (2) direct action of the hormone on bone, causing an increased rate of osseous dissolution, with release of calcium and phosphorus into body fluids. It has also been postulated that there is a third effect of parathyroid hormone—this, on the renal excretion of calcium. Administration of the hormone is thought to raise the renal threshold for calcium; its deficiency lowers the threshold, permitting more calcium to be excreted in the urine.[18]

Hypocalcemia and hyperphosphatemia are the two stimuli for increased parathyroid activity. The former primarily provokes an increase in the bone catabolism effect, thus mobilizing more calcium into the body fluids; the latter stimulates the renal phosphate tubular function, increasing renal excretion of phosphate. The sum total of these two actions is the maintenance of normal serum levels of calcium and phosphorus.

The current theory of the etiology of tetany of the newborn supposes a transient, perhaps physiological, period of hypoparathyroidism.[19-21] This, together with a presumed inefficiency of the clearance of phosphorus due to renal immaturity,[22] permits an increased concentration of serum phosphorus to develop when large phosphorus loads are fed to young infants. Such a load is presented when an infant is fed cow's milk, containing 1220 mg. of calcium and 900 mg. of phosphorus per liter (Ca/P ratio of 1.35:1), in contrast to human milk, which contains 340 mg. of calcium and 150 mg. of phosphorus per liter (Ca/P ratio of 2.25:1). The formula-fed infant will assimilate approximately 1200 mg. of phosphorus per square meter per day, in contrast to the breast-fed infant, who absorbs but 120 mg. per square meter per day.[23]

This tenfold increase in phosphorus absorption is apparently too great a stimulus for the somewhat dormant infantile parathyroids and immature kidneys to handle. Serum phosphorus becomes consequently elevated, and serum calcium, both total and ionized, is depressed.

The exact role of ingestion of small amounts of vitamin D in relation to the pathogenesis of this syndrome is not understood. Recently, however, an increased incidence of hypocalcemia in the newborn period paradoxically has been correlated with various amounts of vitamin D in the formulas.[24] It should also be noted that an occasional case of tetany of the newborn, especially if it is of long duration, may be associated with maternal hyperparathyroidism.[25]

The common signs of tetany of the newborn are hypertonicity, twitchings, and convulsions, these occurring usually at the end of the first week of life. It is of interest, however, that such nonspecific findings as vomiting, cyanosis, and respiratory difficulties are increasingly commoner in association with hypocalcemia during this period. From the laboratory point of view, the low serum calcium concentration is almost always associated with an elevated phosphorus level and a normal BUN concentration in the serum (Table 2). Parenthetically, determination of serum phosphorus can be performed in the laboratory rather quickly. Levels above 7 mg/100 ml. in an infant suspected of tetany would lend great weight to the diagnosis long before the serum calcium level could be ascertained. Since this type of tetany is self-limited, therapy, details of which will be discussed subsequently, is directed toward relief of the immediate symptoms.

TABLE 2.—*Data of Four Typical Infants with "Neonatal Tetany"*

Case	Age of Onset, Days	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.
1	18	6.4	8.5
2	4	6.7	
3	28	7.3	8.5
4	4	7.6	8.0

TABLE 3.—*Summary of Signs and Symptoms of Idiopathic Hypoparathyroidism* *

System or Disease	Signs and Symptoms
Central nervous	Convulsions, mental retardation, intracranial calcification
Respiratory	Stridor, hoarseness, dyspnea
Moniliasis	
Peripheral nervous	Tetany, muscular pain, tremor
Osseous	Increased density of bones
Gastrointestinal	Vomiting, abdominal pain
Ectodermal	Changes in skin, hair, nails, teeth; cataracts
Adrenal hypofunction	

* Based on Forbes.[28]

Postoperative tetany, which was once unheard of in pediatric practice, is now not quite so rare, because of increased interest in the operative removal of the goiter in childhood thyrotoxicosis.

The accepted criteria for the diagnosis of idiopathic hypoparathyroidism have been reduction in the level of serum calcium, elevation of serum phosphorus, a positive phosphorus diuretic response to parathyroid hormone, and exclusion of disease of the systems previously discussed (osseous, gastrointestinal, genitourinary). In addition to the resultant tetany, the symptoms of a patient with idiopathic hypoparathyroidism may be so varied and unrelated that the true diagnosis may be long delayed.[26-28] Table 3 summarizes the findings of Forbes[28] in a series of seven childhood cases. After a perusal of signs and symptoms such as papilledema, laryngospasm, moniliasis, muscle cramps, vomiting, alopecia, cataracts, etc., it is readily understood why the diagnosis of idiopathic hypoparathyroidism may not be immediately apparent. In addition, since the seizures may simulate classical grand mal convulsions, it is not too surprising that many of these patients have been treated for years with antiepileptic medications.

The etiology of the idiopathic variety of hypoparathyroidism is not known. It has been postulated that congenital absence of the parathyroid glands, their degeneration subsequent to trauma, and infection may be factors. Monilial infection has frequently been associated with idiopathic hypoparathyroidism, but it is not clear whether such infection is a cause or a result of the de-

ficiency of the parathyroids. The etiology of the ocular and ectodermal changes of idiopathic hypoparathyroidism is poorly understood, but it is assumed that they are in some manner dependent upon the hypocalcemia. The relationship between the parathyroids and adrenal glands is also perplexing; of great interest in this connection are several reports of adrenocortical insufficiency occurring during the course of hypoparathyroidism.[28,29]

Pseudohypoparathyroidism is a fascinating condition, first described by Albright and co-workers in 1942.[30] Thus far, about 35 cases have been reported, the onset in most instances being in childhood. It has been postulated that the clinical findings in this syndrome are due to a failure of the end-organ, the kidney, to respond with its usual phosphate diuresis to a presumed normal parathyroid hormonal output. This condition is similar to that found in the male Seabright bantam rooster, which has female feathering despite normal testicular androgen output, i. e., the end-organ, feathers, respond in an abnormal manner to a normal hormonal output. Hence, pseudohypoparathyroidism is also known by the alternate mellifluous name, "the Seabright bantam syndrome." Strictly speaking, therefore, it may be argued that this entity should not be classified with disorders of the parathyroid glands but rather with kidney dysfunctions.

A low serum calcium and an elevated serum phosphorus level ("hypoparathyroid chemistries"), a peculiar physical habitus, and an insensitivity to parathyroid hormone compose the triad which is characteristic of pseudohypoparathyroidism. The following is a description of a representative patient whom we have observed for a period of three years.

CASE 6.—A white boy was admitted to Mount Sinai Hospital in November, 1953, at the age of 20 months, because of a peculiar facial appearance coupled with the occurrence of two convulsive episodes during the week preceding admission. Past history revealed that this child was born with a large head and short extremities. During the initial year of life he became progressively more obese; his eyes acquired an exophthalmic appearance, and his development appeared to be retarded.

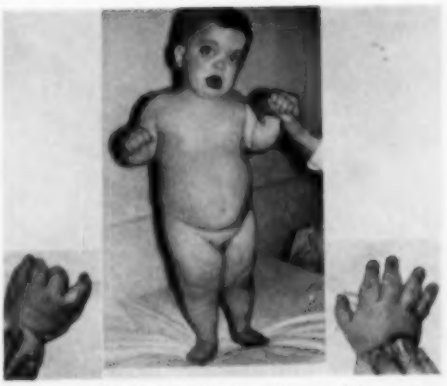

Fig. 4 (Case 6).—Child with pseudohypoparathyroidism, illustrating short, "stubby" figure; round, "pudgy" facies; flat bridge of nose; fat, "bowling-pin shaped" fingers.

Physical examination demonstrated the following features (Fig. 4): chubbiness, large head, exophthalmos, flat nasal bridge; teeth were small and irregularly shaped; the hands were fat, with short stubby "bowling-pin"-shaped fingers. The feet were also fat, and the middle toes on each foot were longer than the second toes. Bilateral papilledema was present. Achondroplasia and an intracerebral space-occupying lesion were first considered as diagnoses, but during observation laryngeal stridor became a prominent symptom. Chemical examination of the serum revealed the characteristic low calcium and elevated phosphorus levels. These findings, together with the clinical features mentioned, suggested the diagnosis of pseudohypoparathyroidism. Roentgen examination (Fig. 5) showed the characteristic short, thick phalanges and the shortened, hypoplastic first metacarpal (similar changes were present in the bones of the feet). The bones of the calvarium were also thickened. The results of the Ellsworth-Howard test, the confirmatory diagnostic procedure, were typical of those found in patients with pseudohypoparathyroidism. This test was performed by administering 50 units of parathyroid extract intravenously, measuring the hourly urinary phosphate output, and comparing the results so obtained with those found during suitable control periods. Figure 6 contrasts the response of our patient to that of a normal child, that of a child with idiopathic hypoparathyroidism, and that of a patient with "complete" pseudohypoparathyroidism.[31] Although there is a partial phosphate diuresis in the patient under discussion, it is clear that this response is far smaller than the tenfold increase in phosphate excretion which occurs in a

Fig. 5 (Case 6).—*A*, roentgenogram of hand of patient with pseudohypoparathyroidism. Note coarse trabeculation of metacarpals and phalanges; shortened, underdeveloped metacarpals, especially that of the thumb; tendency toward invagination of epiphyses of metacarpals and phalanges into the shafts. *B*, roentgenogram of skull, showing brachycephalic skull, with thickening of the bones of the calvarium.

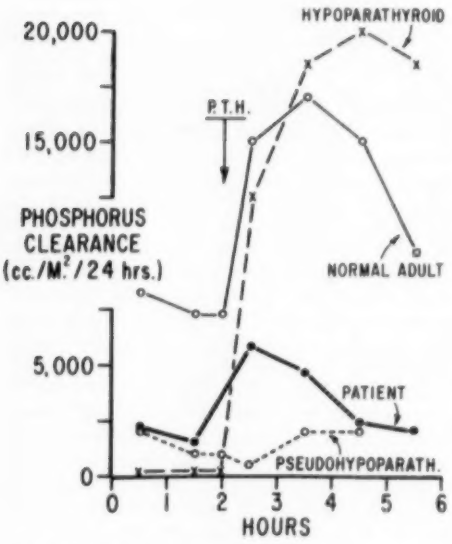

Fig. 6.—Partial urinary phosphorus response to intravenous administration of parathyroid extract (P. T. H.) (Ellsworth-Howard test) of patient with pseudohypoparathyroidism (Case 6) compared with that of normal adult patient with idiopathic hypoparathyroidism and patient with "complete" pseudohypoparathyroidism.

true hypoparathyroid patient. Figure 7 depicts the therapy and course of our patient with pseudohypoparathyroidism. It is of interest that the papilledema disappeared rapidly within two months after serum calcium concentration had returned to normal levels.

Comment: Despite the maintenance of normal levels of serum calcium and phosphorus for three years, certain of the physical stigmata (the obesity, the facies, and

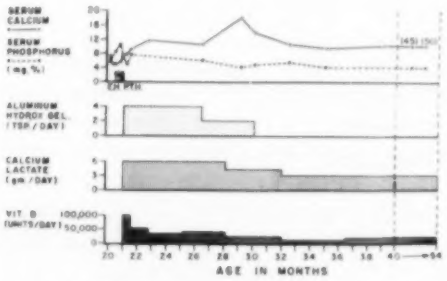

Fig. 7 (Case 6).—Laboratory data, therapy, and course of patient with pseudohypoparathyroidism followed for 34 months. Two arrows labeled E. H. indicate performance of Ellsworth-Howard tests; bar labeled P. T. H. indicates five-day course of parathyroid hormone therapy, which induced partial return of serum calcium and phosphorus concentrations to normal; figures in parentheses indicate months at which serum determinations were performed.

the configuration of the fingers) have persisted. The problem of the eventual mental development of this child remains undetermined, but it should be noted that most of the reported patients have been retarded.[32] The possibility that a normal serum calcium concentration is essential for normal cerebral function seems to warrant some consideration. Prolonged follow-up of our patient may yield information on this very intriguing speculation.

E. Miscellaneous.—In the category of hypocalcemias unclassified as to exact etiology is included neonatal or "first-day" hypocalcemia. Newly reported by at least two groups of workers[33,34] is the syndrome of low serum calcium concentration on the first day of life associated usually with some complication of pregnancy, such as prematurity, maternal diabetes, placenta previa, or premature separation of the placenta. Although this clinical picture is now being found with greater frequency in other pediatric centers, it is not known whether this condition is a variant of classical infantile tetany which usually occurs several days after birth. Furthermore, its relationship to prematurity and the various complications of pregnancy with which it appears to be associated is not understood. Finally, whether the hypocalcemia is cause or effect of some of the frequently associated nonspecific signs and symptoms, such as respiratory difficulty, cyanosis, abdominal distention, edema, etc., is not clear at this time. Further studies of the prevalence of "first-day hypocalcemia" coupled with controlled therapeutic trials are needed to shed light on these various questions.

Alkalosis rarely causes tetany in childhood, but it should at least be mentioned. It is still uncertain if alkalosis, whether due to persistent vomiting, increased pulmonary ventilation, or administration of sodium bicarbonate, causes an actual decrease in serum ionizable calcium.[35] The prevailing opinion is that the tetany caused by this acid-base disturbance, while not associated with a decrease of total serum calcium, is due to a decrease in the level of the ionizable calcium. Other factors, such as alteration of the balance among the various ions in the blood, sodium, potassium, magnesium, and hydrogen, as well as calcium, may be involved.[36] Therapy of this form of tetany should obviously be directed toward alteration of the cause of the alkalosis.

Finally, for the sake of completeness, the syndrome of tetany due to low serum concentration of magnesium should be included.[37] The clinical manifestations of this type of tetany are apparently not related to the serum calcium level; nevertheless, they are identical with those resulting from hypocalcemia.

Treatment of Hypocalcemia

Treatment of hypocalcemia in general will be discussed, and the specific therapy of the previously mentioned clinical syndromes will be described.

Three classes of agents are available for raising the concentration of serum calcium and for maintaining it at normal levels. These are calcium salts, parathyroid hormone-activated sterol compounds, and aluminum hydroxide gel preparations. The most direct method of elevating serum calcium is the administration of one of the calcium salts. For emergency treatment, a 10% solution of calcium gluconate may be given intravenously at a rate not to exceed 1 cc. per minute. Careful observation of the child is essential, and the injection should be discontinued at the first sign of bradycardia or as soon as the desired clinical result is obtained. It is important to prevent leakage of calcium gluconate into the tissues surrounding the vein, since calcium salts are very irritating and may cause necrosis. (Calcium should never be administered intramuscularly.) It should also be noted that calcium salts must be administered with great caution to a child who has received digitalis, since the calcium ion may potentiate the effect of this drug.[38,39]

Normal calcium levels in serum may also be maintained by one of several calcium

salts administered orally. It is usually best to initiate therapy with calcium chloride. This salt contains the greatest percentage of calcium (36%), and its acid character enhances calcium absorption from the gastrointestinal tract. Calcium chloride must be administered in a solution which does not contain more than 1% to 2% of the salt by weight, since greater concentrations may irritate the gastrointestinal mucosa. This salt also should not be continued for longer than 48 hours, because its acidifying properties may promote a systemic acidosis. Doses of 1.5 to 3 gm. daily are recommended; the desired concentration may be obtained by placing 0.5 to 1.0 gm. of powdered calcium chloride in every other bottle of formula. Treatment may be continued with calcium lactate, which contains 18% calcium, or with calcium gluconate, which contains 9% calcium. The recommended dose of these salts is 3 to 6 gm. daily.

Therapy with calcium salts alone is especially valuable in the more acute forms of tetany, such as those described as being associated with the postacidotic state, hypertonic dehydration, and acute pancreatitis. Tetany of the newborn, postoperative tetany, and "first-day hypocalcemia" may also be controlled chiefly by calcium salts.

Parathyroid hormones and the two commonly employed activated sterols, vitamin D and dihydrotachysterol, have two main actions[40]: enhancement of urinary phosphorus excretion and promotion of absorption of calcium by the gastrointestinal tract. The three compounds vary in their ability to accomplish these actions, parathyroid hormone being the more potent phosphate diuretic, and vitamin D, the strongest promoter of calcium absorption, with dihydrotachysterol holding an intermediate position. The total effect of all three agents, however, is elevation of serum calcium and lowering of serum phosphorus, making them useful drugs in the therapy of hypocalcemia.

From the practical standpoint, parathyroid hormone has very little or no use in therapy. Parathyroid hormone preparations which are commercially available are impure; potency of different lots varies, and resistance to the effect of the hormone develops rapidly. Vitamin D and dihydrotachysterol are approximately equally effective, but preparations of the former are less expensive and are more easily standardized. Thus, vitamin D is the more commonly used agent in practice. Dosage varies, but the general rule is to administer large doses for the first few days of therapy (100,000 to 500,000 units daily)§ and to reduce the dose later as the serum calcium concentration approaches the normal range. Subsequent dosage is regulated at the minimum level necessary for maintenance of normal serum calcium, the exact dose being titrated by means of frequent serum calcium and urine calcium (Sulkowitch) determinations‖ (doses of 15,000 to 50,000 units of vitamin D are average). Periodic renal-function tests are necessary to detect kidney damage which may occur when continued vitamin D therapy, even at the lower dosage levels, is employed.

Vitamin D therapy is especially valuable where prolonged maintenance of normal calcium level may be necessary, as in idiopathic hypoparathyroidism or pseudohypoparathyroidism. In renal disease it is also of some value, but it is required in much smaller doses than are cited above.

Finally, aluminum hydroxide gel is a useful aid in maintaining normal serum calcium.[42] Several preparations are available from different pharmaceutical firms

§ A special high-potency oral preparation which contains 2000 units of vitamin D per drop, prepared by Endo Products, Inc., and supplied by Dr. Samuel M. Gordon is being used.

‖ The Sulkowitch reagent[41] is composed of 2.5 gm. of oxalic acid, 2.5 gm. of ammonium oxalate, 5.0 cc. of glacial acetic acid, and distilled water up to 150 cc. Addition of 2 cc. of the reagent to 5 cc. of urine will produce a cloudy precipitate of calcium oxalate, the intensity of which will vary with amount of calcium being excreted in the urine. Parents of children under therapy can be taught to perform the test each morning prior to breakfast and to report if a consistent daily increase of calcium excretion appears, thus aiding in the regulation of therapy.

(Amphojel, Basaljel, Gelusil, and others). The aluminum of these compounds combines with phosphate ion in the gastrointestinal tract to form an insoluble aluminum phosphate which is excreted in the stool. Diminished phosphorus absorption will tend to lower the serum phosphorus and thus facilitate elevation of serum calcium. The aluminum gels are valuable for infants and children, because the large quantity of milk in their diet results in a high phosphorus intake. The dose of aluminum gel recommended for infants and children is 15 to 90 ml. daily. A commonly used mixture consists of 10 gm. of calcium lactate in 100 ml. of aluminum hydroxide gel (Amphojel), administered in doses of 15 to 30 ml. three times a day.[43]

It can be seen from the above discussion and from the clinical examples presented that prolonged therapy of hypocalcemia may be accomplished by the use of calcium salts, together with vitamin D and aluminum hydroxide gel. As the serum calcium level approaches normal, the aluminum compounds may be discontinued first, because they tend to cause constipation.¶ Next, the vitamin should be titrated downward and, finally, the calcium salts may be reduced. With this type of therapy and with careful observation, control of the serum calcium level is not difficult.

Summary and Conclusion

By means of typical examples, an attempt has been made to illustrate the variety of clinical conditions with which hypocalcemia may be associated and the heterogeneity of signs and symptoms by which it may be manifested. It is only by keeping hypocalcemia in mind, and by determining the serum calcium concentration whenever this condition is a possibility, that the diagnosis will be made and proper therapy instituted.

¶ Gelusil, which contains magnesium trisilicate in addition to aluminum hydroxide, may be of particular advantage, since it is less likely to cause constipation than other aluminum preparations.

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REFERENCES

1. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941.

2. Eliot, M. M., and Park, E. A.: Rickets, in Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 1, Chap. 36, p. 104.

3. Crawford, J. D.; Gribetz, D., and Talbot, N. B.: Mechanism of Renal Tubular Phosphate Reabsorption and the Influence Thereon of Vitamin D in Completely Parathyroidectomized Rats, Am. J. Physiol. 180:156, 1955.

4. Wexler, I. B.; Pincus, J. B.; Natelson, S., and Lugovoy, J. K.: The Fate of Citrate in Erythroblastotic Infants Treated with Exchange Transfusion, J. Clin. Invest. 28:474, 1949.

5. Bunker, J. P.; Stetson, J. B.; Coe, R. C.; Grillo, H. C., and Murphy, A. J.: Citric Acid Intoxication, J. A. M. A. 157:1361, 1955.

6. Rapoport, S.; Dodd, K.; Clark, M., and Sylm, I.: Postacidotic State of Infantile Diarrhea: Symptoms and Chemical Data: Postacidotic Hypocalcemia and Associated Decreases in Levels of Potassium, Phosphorus and Phosphatase in the Plasma, Am. J. Dis. Child. 73:391, 1947.

7. Finberg, L., and Harrison, H. E.: Hypernatremia in Infants, Pediatrics 16:1, 1955.

8. Weil, W. B., and Wallace, W. M.: Hypertonic Dehydration in Infancy, Pediatrics 17:171, 1956.

9. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Disease, Baltimore, Williams & Wilkins Company, 1948, p. 223.

10. Patterson, P., in Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953, p. 515.

11. Edmondson, H. A., and Berne, C. J.: Calcium Changes in Acute Pancreatic Necrosis, Surg. Gynec. & Obst. 79:240, 1944.

12. Merrill, J. P.: The Treatment of Renal Failure, New York, Grune & Stratton, Inc., 1955, p. 33.

13. Butler, A. M.; Wilson, J. L., and Farber, S.: Dehydration and Acidosis with Calcification at Renal Tubules, J. Pediat. 8:489, 1936.

14. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Disease, Baltimore, Williams & Wilkins Company, 1948, p. 227.

15. Lightwood, R.; Payne, W. W., and Block, J. A.: Infantile Renal Acidosis, Pediatrics 12:628, 1953.

16. Dent, C. E.: Rickets and Osteomalacia from Renal Tubule Defects, J. Bone & Joint Surg. 34-B: 266, 1952.

17. Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth Through Adolescence, Boston, Harvard University Press, 1952, p. 91.

18. Talmage, R. V.: Studies on the Maintenance of Serum Calcium Levels by Parathyroid Action on Bone and Kidney, Ann. New York Acad. Sc. 64:326, 1956.

19. Pincus, J. B., and Gittleman, I. F.: Infantile Tetany: A Metabolic Study, Am. J. Dis. Child. 51:816, 1936.

20. Gardner, L. I.; MacLachlin, E. A.; Pick, W.; Terry, M. L., and Butler, A. M.: Etiologic Factors in Tetany of Newly Born Infants, Pediatrics 5:228, 1950.

21. Gardner, L. I.: Tetany and Parathyroid Hyperplasia in the Newborn Infant: Influence of Dietary Phosphate Load, Pediatrics 9:534, 1952.

22. McCrory, W. W.; Forman, C. W.; McNamara, H., and Barnett, H. L.: Renal Excretion of Phosphate in Newborn Infants: Observations in Normal Infants and in Infants with Hypocalcemic Tetany, Am. J. Dis. Child. 80:512, 1950.

23. Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth Through Adolescence, Boston, Harvard University Press, 1952, p. 116.

24. Gittleman, I. F., and Pincus, J. G.: Influence of Diet on the Occurrence of Hyperphosphatemia and Hypocalcemia in the Newborn Infant, Pediatrics 8:778, 1951.

25. Walton, R. L.: Neonatal Tetany in 2 Siblings: Effect of Maternal Hyperparathyroidism, Pediatrics 13:227, 1954.

26. Steinberg, H., and Waldron, B. R.: Idiopathic Hypoparathyroidism: An Analysis of 52 Cases, Including Report of a New Case, Medicine 31:133, 1952.

27. Harrison, H. E.: Idiopathic Hypoparathyroidism, Pediatrics 17:442, 1956.

28. Forbes, G. B.: Clinical Features of Idiopathic Hypoparathyroidism in Children, Ann. New York Acad. Sc. 64:432, 1956.

29. Papadatos, C., and Klein, R.: Addison's Disease in a Boy with Hypoparathyroidism, J. Clin. Endocrinol. 14:653, 1954.

30. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudohypoparathyroidism: An Example of "Seabright-Bantam Syndrome; Report of 3 Cases, Endocrinology 30:922, 1942.

31. Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth Through Adolescence, Boston, Harvard University Press, 1952, p. 109.

32. Frame, B., and Carter, S.: Pseudohypoparathyroidism: Clinical Picture and Relation to Convulsive Seizures, Neurology 5:297, 1955.

33. Gittleman, I. F.; Pincus, I. B.; Schmerzler, E., and Saito, M.: Hypocalcemia Occurring on the First Day of Life in Mature and Premature Infants, Pediatrics 18:721, 1956.

34. Bruck, E., and Weintraub, D. H.: Serum Calcium and Phosphorus in Premature and Full-Term Infants: A Longitudinal Study in the First 3 Weeks of Life, A. M. A. Am. J. Dis. Child. 90:653, 1955.

35. Yannet, H.: The Effects of Alkalosis on the Relationship Between Serum Calcium and Protein in Vivo, J. Biol. Chem. 137:409, 1941.

36. Kramer, B., and Leibner, I. W.: Tetany: Biochemical and Clinical Considerations, M. Clin. North America 36:875, 1952.

37. Miller, J. F.: Tetany Due to Deficiency in Magnesium: Its Occurrence in a Child of 6 Years with Associated Osteochondrosis of Capital Epiphysis of Femur (Legg-Perthes Disease), Am. J. Dis. Child. 67:117, 1944.

38. Gold, H., and Edwards, D. J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, Am. Heart J. 3:45, 1927.

39. Smith, R. M.: Blood Replacement in Thoracic Surgery for Children, J. A. M. A. 161: 1124, 1956.

40. Albright, F.; Barnett, C. H.; Parson, W.; Reifenstein, E. C., and Roos, A.: Osteomalacia and Late Rickets, Medicine 25:399, 1946.

41. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, J. Urol. 37:746, 1937.

42. Shorr, E., and Carter, A. C.: Aluminium Gels in the Management of Renal Phosphatic Calculi, J. A. M. A. 144:1549, 1950.

43. Cooke, R. E.: Personal communication to the author.

Case Reports

Apparently Unilateral Polycystic Kidney

A Cause for Abdominal Calcific Shadows

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Polycystic disease of the kidney, according to some authors, is always bilateral.[1] Others state that it may be unilateral.[2] In the bilateral form, which in some instances seems to have a hereditary tendency, there appear to be two types: (*a*) the more frequent adult form, characterized by replacement of renal parenchyma and distortion of the collecting tubules due to large cysts, with death usually occurring in the fifth to sixth decade; (*b*) the infantile form, in which small cysts are present throughout the parenchyma and replacement of renal tissue leads to early death of the patient.

A unilateral variety which is said to be congenital has been described in both adults and children. In some of these cases of presumed unilateral polycystic disease there has been postmortem confirmation[3,4]; in others, further study has demonstrated that the involvement was actually bilateral.[5] A review of the literature shows that the terms unilateral polycystic, unilateral multicystic, and multilocular cystic have been used to describe pathologically and clinically similar cases.[6-19] Because of confused terminology and since there is a lack of reliable information concerning the ultimate fate of the contralateral kidney, it is recommended that the term "apparently unilateral" polycystic disease be used in all such cases.

This case report and brief review of the literature is presented to show unusual features in one case and in an attempt to clarify the confusion in the literature with regard to clinical usage of various terms relating to cystic disease of the kidney.

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Report of Case

The patient was born on Dec. 4, 1955, weighing 3440 gm. Delivery was uneventful, and the immediate neonatal condition was good. Examination showed only a mild calcaneovalgus deformity of the left foot. The infant was discharged from the newborn nursery on Dec. 10 in good condition.

She was seen again at the age of one month, at which time no abnormalities on physical examination were noted, with the exception of an umbilical polyp. A small quantity of iodized oil (Lipiodol) was injected into this polyp to exclude an omphalomesenteric duct remnant, and on the plain roentgenogram of the abdomen several well-defined areas of calcification were noted in the region of the right kidney, but the soft tissue outlines of the kidney were not well identified (Fig. 1).

The infant was lost to follow-up until the age of 4 months. At that time an intravenous pyelogram was done in an effort to determine the location of the calcification previously seen. These roentgenograms showed no kidney function on the right but revealed normal function and structure on the left (Fig. 2).

The infant was then admitted to Doernbecher Hospital for further urologic work-up. The physical examination was normal. No abdominal masses were palpated. The blood pressure was not recorded.

Laboratory examinations: The urinalysis was normal. The BUN was 15 mg. per 100 cc. The serum Ca and P were 11 and 6.8 mg. per 100 cc., respectively. Total serum protein was 5.3 gm. per 100 cc. (albumin 3.8 gm. and globulin 1.5 gm.). The hemogram revealed 12.3 gm. per 100 cc. of hemoglobin; 10,850 WBC, with a normal differential count. The sedimentation rate was normal. Cystoscopy was performed on April 6, 1956. A No. 4 ureteral catheter could not be passed more than a few centimeters up the right ureter. After injection of a contrast agent, radiography demonstrated the lower right ureter but showed

Fig. 1.—Discrete well-defined areas of calcification are shown in the region of the right kidney.

no communication with the renal pelvis. The cystogram revealed a normal bladder contour, without reflux on either side. On April 17, 1956, the right kidney was explored through a right flank incision. The kidney was found to be almost entirely replaced by multiple bluish cysts ranging in size from 1 to 7 mm. A calcified body, apparently a phlebolith, was seen in the renal vein as it emerged from the hilum of the kidney. The ureter was ligated 3 cm. below the ureteropelvic junction. The renal pedicle was ligated, and the kidney was removed. The left kidney was not visualized. No abnormality of the liver was noted at surgery.

Pathology: The kidney weighed 10 gm. and measured 5×3×2 cm. (Fig. 3). Histopathologic sections showed multiple irregular-sized subcortical cysts each lined by a single layer of flattened cells and surrounded by a fibrous wall. No glomeruli could be seen within the cystic wall. The remaining cortex contained a considerable number of normal-appearing glomeruli as well as convoluted tubules. Diffuse and periductal fibrosis was present at the medullary area, associated with patchy round-cell infiltration. This was most prominent at the ductal zone, where several islets of cartilage were also seen. Several branches of the renal vein were obliterated by organized phleboliths (Fig. 4). Grossly, the ureter could not be well identified. The pelvis and calyces were slightly dilated; however, the mucosa was smooth and glistening.

Fig. 2.—This is a 10-minute film of an intravenous pyelogram. Left kidney is normal; there is no evidence of function on the right, even in a delayed film.

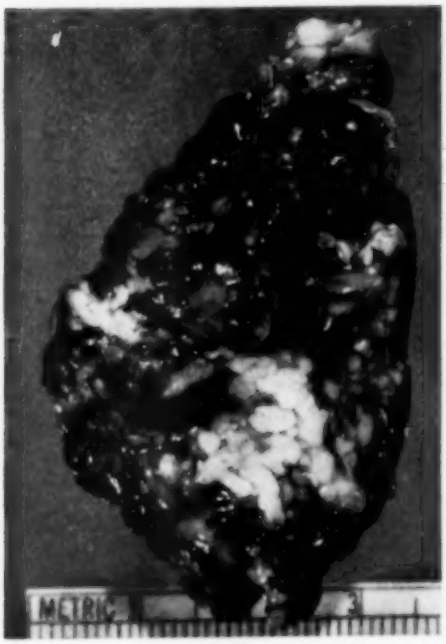

Fig. 3.—Photograph of the excised kidney. Weight, 10 gm.; size, 5×3×2 cm.

Fig. 4.—X-ray of excised specimen, showing well-defined calcification of the phleboliths.

Comment

In addition to having a confused terminology, cystic disease of the kidney is poorly defined as to etiology and pathogenesis.

"Unilateral multicystic kidney" was a term first used by Schwartz to describe a cystic kidney in a 4-month-old infant; a follow-up period of 14 months showed no gross abnormality in the contralateral kidney. The pathologic features of the removed kidney were not unlike those in descriptions of "polycystic" kidneys as given by other authors. Since Schwartz's report there have been numerous isolated case reports of unilateral polycystic kidney. Unfortunately, these reports have brought about a great deal of confusion regarding differentiation between multilocular cysts of the kidney and multicystic or polycystic kidney; some cases of polycystic kidney have been reported as multilocular cystic kidneys and vice versa.[9,16] Pathologic differentiation between multilocular cystic and polycystic disease of the kidney is well defined, but how this differentiation bears on the ultimate prognosis is not known.

The diagnosis of a unilateral polycystic kidney with clinical evidence that the contralateral kidney is not involved cannot be accepted until the apparently normal kidney has been examined pathologically or by the indirect method of long-term follow-up. Barnett[5] reported nine cases of unilateral "polycystic" kidney and five years later in a subsequent report stated that five of these had involvement of the contralateral kidneys. The only other report that included a follow-up period of impressive length (14 years) was a case reported as unilateral multicystic kidney but described pathologically as a kidney with multilocular cysts.[16] Bugbee and Wollstein[20] found 4 cases of unilateral polycystic kidney in 4903 postmortem examinations in infants, whereas Bell[3] reported an incidence of 11 cases of unilateral polycystic kidney in 32,360 postmortem examinations which included adults (proportion of children to adults not given). This

difference appears to be significant and suggests that in some patients unilateral polycystic disease of the kidney eventually becomes bilateral. Oppenheimer [4] felt strongly that most cases of unilateral polycystic disease would subsequently become bilateral and stressed the difficulty of evaluation of the "normal" kidney at the time of surgery.

Bilateral polycystic disease is frequently associated with other congenital anomalies, and this is also true of the unilateral form. Ten of the twenty-seven case reports [6-13,16-19] showed abnormalities of the ureter or renal pedicle—the ureteric opening may be absent or the ureter may be atretic, especially in the upper third, where it may be represented by a fibrous cord; the renal pedicle may be absent. An undescended testicle was adherent to the cystic mass in two instances.

Twenty-one of the twenty-seven cases presented with a mass in the flank. Twenty-two of the patients were children, and twenty of these twenty-two were investigated because of a mass. One case showed hypertension which was relieved by nephrectomy. The majority of the cases in which excretory urography was performed showed no function on the affected side. Some showed reduced function.

Calcification in the renal artery as part of generalized arteriosclerosis is common but as an isolated finding is rare. Fish and Hallock [21] described abnormal calcifications in the kidney which were thought to be calculi but subsequently at postmortem examination were found to be in the renal arterial system. Stirling and Lawrence [22] reported a case of calcification in one of the branches of the renal vein. Willson-Pepper and Slade [12] described the case of a 7-year-old girl who had flake-like areas of parenchymal calcification in a unilateral polycystic kidney which was preoperatively thought to be the site of a malignancy. The pathologic findings in cases which showed no function on excretory urography and in those which showed reduced or normal function were identical. "The kidneys are usually larger than normal but may be small. The surface is composed of many cysts of varying size. At microscopy in addition to cysts which vary markedly in size there are isolated little islands of nephrons in different stages of atrophy separated by a stroma far more abundant than the usual infantile or adult forms of congenital polycystic kidney. Small foci of hyaline cartilage may be seen in relation to these units. These unilateral polycystic kidneys may be markedly diminished in size with much fibrosis, calcification, and even ossification. Often the collecting tubules are rudimentary and are characteristically lined with tall epithelium." [2] The differential diagnosis of unilateral renal masses in children includes Wilms' tumor, neuroblastoma, mesenteric cysts, hydronephrosis, polycystic kidneys, and other nonrenal peritoneal masses. With the aid of urologic work-up a definite preoperative diagnosis sometimes can be made.

Summary

It seems apparent that most instances of apparently unilateral polycystic kidney occur in otherwise healthy and young children. When a child presents with a flank mass which proves to be a calcium-containing nonfunctioning kidney with associated ureteral or other anomalies, the likelihood of polycystic kidney should be considered. Owing to the incomplete understanding of this condition, an accurate prognosis is difficult to make without long-term follow-up to insure that there is no involvement of the contralateral kidney.

Drs. D. E. Pickering and C. T. Dotter helped in the preparation of this article.

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REFERENCES

1. Shanks, S. C., and Kerley, P., Editors: A Text-Book of X-Ray Diagnosis by British Authors in 4 Volumes: Vol. 3, Ed. 2, Philadelphia, W. B. Saunders Company, 1950, p. 761.

2. Allen, A. C.: The Kidney, New York, Grune & Stratton, Inc., 1951.

3. Bell, E. T.: Cystic Disease of the Kidneys, Am. J. Path. 11:373 (May) 1935.

4. Oppenheimer, G. D.: Polycystic Disease of the Kidney, Ann. Surg. 100:1136 (Dec.) 1934.

5. Barnett, C. E.: Polycystic Kidney, in Transactions of the Section on Genito-Urinary Diseases, Chicago, American Medical Association, 1917, p. 185.

6. Spence, H. M.: Unilateral Multicystic Kidney, J. Urol. 75:693 (Dec.) 1955.

7. Ravich, A.: Predominately Unilateral Polycystic Kidneys, Urol. & Cutan. Rev. 41:566 (Aug.) 1937.

8. Duncan, I. G.: Removal of a Polycystic Kidney from a Baby 2 Months of Age, Memphis M. J. 21:119 (Aug.) 1946.

9. Randolph, M., and Murphy, F.: Congenital Multilocular Cysts in a Newborn Infant, Clin. Proc. Child. Hosp. 3:248 (Sept.) 1947.

10. Dakin, W. A.: Unilateral Multilocular Cystic Kidney, Canad. M. A. J. 42:531 (June) 1940.

11. Berman, L. S., and Oweida, N.: Nephrectomy for Unilateral (?) Polycystic Kidney Disease, M. Ann. District of Columbia 24:354 (July) 1955.

12. Willson-Pepper, J. K., and Slade, D. A.: Calcification of a Polycystic Kidney, Brit. J. Urol. 27:172 (June) 1955.

13. Wagner, J. A., and Toulson, W. H.: Encapsulated Multilocular Serous Cysts of the Kidney Associated with Hypertension: Occurrence in a 19 Month Old Infant, Bull. School Med. Univ. Maryland 26:177 (Jan.) 1942.

14. Wells, C.: Polycystic and "Unilateral Polycystic Kidney: Review of Literature and Two Cases, One with Intracystic Papilloma, Brit. J. Urol. 8:22 (March) 1936.

15. Baretz, L. H., and Baron, P.: Congenital Cystic Disease of the Kidney, New York J. Med. 53:208 (Jan. 15) 1953.

16. Lynch, R. D., and Thompson, R. F.: Unilateral Multicystic Kidney, J. Urol. 38:58 (July) 1937.

17. Oppenheimer, G. D., and Narins, L.: Unilateral Polycystic Kidneys, J. Urol. 61:866 (May) 1949.

18. Lih, H., and Waud, R. D.: Unilateral Polycystic Kidney in a Newborn, J. Urol. 68:60 (July) 1952.

19. Schwartz, J.: An Unusual Unilateral Multicystic Kidney in an Infant, J. Urol. 35:259 (March) 1936.

20. Bugbee, H. G., and Wollstein, M.: Surgical Pathology of the Urinary Tract in Infants: Based on a Review of 4903 Necropsies, J. A. M. A. 83: 1887 (Dec. 13) 1924.

21. Fish, G. W., and Hallock, L. A.: Calcification of Intrarenal Arteries Giving Roentgen Appearance of Calculi, J. A. M. A. 96:1935 (June 6) 1931.

22. Stirling, W. C., and Lawrence, C. S.: Calcification of Renal Vein with Bilateral Nephrolithiasis: Report of Case, J. A. M. A. 82:25 (Jan. 5) 1924.

23. Goldstein, A. E., and Abeshouse, B. S.: Calcification and Ossification of the Kidney: Review of Literature and Report of Cases, Radiology 30:544 (May) 1938; abstracted, J. A. M. A. 111: 207 (July 9) 1938.

Neonatal Hepatitis in One of Binovular Twins

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This case report is presented in order to shed further light on the etiology and transmission of neonatal hepatitis. This is the second case of neonatal hepatitis reported in one of fraternal twins.[1] This is the first case reported that was recognized during the course of the illness. In the present case the abnormal placenta gives us more information about the transmission of the disease.

Report of Case

The mother was a healthy 19-year-old primigravida. Her history included the usual childhood illnesses. At the age of 15 years she had a febrile illness of six weeks' duration associated with generalized adenopathy, which was tentatively diagnosed as infectious mononucleosis. During that illness numerous venipunctures were made and she also received many parenteral injections. She had never been jaundiced or exposed to hepatic toxins, nor was there any history of syphilis. There was no history of transfusions. Her blood type was O, Rh-positive.

Her twins were born by cesarean section on Aug. 13, 1956. The first twin was a boy weighing 5 lb. 6½ oz. He had to be resuscitated but breathed within two minutes. The placenta of this first twin was pale and small and had much fibrosis at the periphery. The other twin weighed 8 lb. 11½ oz., needed no resuscitation, and had a separate normal-appearing placenta. Five hours after delivery the first twin was noted to be slightly jaundiced. During the next two days the infant became progressively more jaundiced and lethargic and was very difficult to feed. On the third day periods of apnea began and petechiae appeared on the chest. The liver and spleen were markedly enlarged. At this point, a blood culture was taken and the child was given antibiotics, intravenous fluids, and vitamin K. With this regimen the child improved to the point where the respirations became normal; the bleeding tendency disappeared, but he continued to be a feeding problem, and the jaundice continued to increase in intensity. The blood culture was negative for growth. The infant's blood type was O, Rh-positive, the direct and indirect Coombs tests were negative; the serologic test was negative, and the hemoglobin was consistently over 20 gm. The white cell count and differential count were normal for his age. On Aug. 16, at 3 days of age, the total bilirubin was 19 mg. per 100 cc. Examination of the feces was negative for stercobilinogen, and examination of the aspirated stomach contents was negative for bile. The urine contained bile but only a trace of urobilinogen. At 7 days of age the bilirubin was 30 mg. per 100 cc., 24.5 mg. being direct-reacting and 5.5 mg., indirect-reacting. X-rays of the chest revealed some nodularity in both lung fields, but this cleared in a period of several days. X-rays of the skull were normal.

At 9 days of age the child was transferred to another hospital with what appeared to be a progressive, obstructive jaundice. On admission the child was found to be moderately lethargic, slightly dehydrated, and deeply jaundiced, but he was in no severe distress. The liver edge was firm and 7 cm. below the costal margin. The spleen was firm and 5 cm. below the costal margin. At 14 days of age the bilirubin was 27.7 mg. per 100 cc., with 20.8 mg. direct-reacting and 6.9 mg. indirect-reacting. At this time urobilinogen began to appear in the stools in increasing amounts. At 16 days of age the bilirubin had dropped to 26 mg. per 100 cc., 20.8 mg. direct-reacting and 5.2 mg. indirect-reacting. The cephalin-flocculation test was negative on several occasions.

In view of the laboratory changes, especially the failure of the bilirubin to show a steady rise, it was now felt that this was a case of nonobstructive hepatocellular jaundice. Steroids were then begun as a cholegogue. With the inception of steroid therapy the jaundice began to clear dramatically, so that at 18 days of age the bilirubin was down to 17.5 mg. per 100 cc., most of it being direct-reacting. By 22 days of age the bilirubin was down to 12.8 mg. and by 25 days of age the bilirubin was 2 mg. per 100 cc. and the steroids were discontinued. The child was now gaining weight, feeding well, and normally active and had a minimal amount of jaundice. On his discharge from the hospital the liver was still enlarged to 4 cm. below the costal margin and the spleen remained slightly enlarged, about 2 cm. below the costal margin.

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The child was seen again in my office at 7 weeks of age. The liver was now slightly smaller, about 3 cm. below the costal margin, and the spleen was barely palpable. A moderate clinical jaundice had reappeared since the discharge from the hospital, and the bilirubin had again became elevated, to 9.1 mg. per 100 cc., 7.5 mg. being direct-reacting. The cephalin-flocculation test was again negative. A moderate anemia (hemoglobin 11 gm.) was present. The heterophil test, Toxoplasma complement-fixation test, and malaria smears were all negative. Two weeks later, without further treatment, the jaundice had cleared completely. The spleen and liver were barely palpable. The bilirubin was normal, and the child seemed to be in good health. By 7 months of age the child was doing very well. He weighed 16½ lb., and the liver and spleen were no longer palpable. Motor and social development were normal.

Investigation of the other twin revealed a normal infant with a negative Toxoplasma complement-fixation test. Six weeks after delivery the mother seemed to be in good health, without any complaints. A cephalinflocculation test on the mother's serum revealed a 2+ reaction, while the sulfobromophthalein (Bromsulphalein)-retention test was normal. Toxoplasma complement-fixation test on the mother's serum was also negative. At 7 months a repeat cephalin-flocculation test on the mother's serum was again 2+, while the thymol turbidity was 2 Maclagan units.

Comment

The 2+ cephalin-flocculation reactions on the mother's serum may be an indication of abnormal liver function and suggest that the mother not only may be a carrier of serum hepatitis but also may have mild liver dysfunction. However, this test is nonspecific enough to be misleading in this respect. Stokes and others[2,3] have pointed out that the carrier of serum hepatitis usually does not have a history of jaundice and that those carriers with abnormal liver function, as revealed by laboratory tests, are in the minority. The finding of normal liver-function tests in the affected twin is also consistent with the diagnosis of hepatitis, since in infancy hepatitis usually produces no changes in these tests.

Stokes et al.[4] were the first to advance evidence that neonatal hepatitis was due to transplacental transmission of a virus, probably the serum homologous type. More recently case reports have appeared of two or more siblings who incurred the disease.[1,5,6] One of these reports was of three cases of neonatal hepatitis in siblings with a normal sibling born between the affected ones. This has suggested that either local placental factors allowed transmission of the virus or that a recurrent or fluctuating viremia was present in the mother. The present case favors the former hypothesis, especially in view of the abnormal placenta in the affected twin and the apparently normal placenta in the unaffected child.

A review of the reported cases reveals a significantly high mortality in this disease. The marked improvement in this case after steroids were started suggests that further trial with steroids in neonatal hepatitis is indicated.

Summary

A case of neonatal hepatitis developing in one of binovular twins is presented.

The degenerative changes of the placenta in the affected twin may be the explanation of why only one twin contracted the disease.

The treatment of this disease with adrenal steroids is emphasized.

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REFERENCES

1. Gellis, S. S.; Craig, J. M., and Hsia, D. Y. Y.: Prolonged Obstructive Jaundice in Infancy: IV. Neonatal Hepatitis, A. M. A. J. Dis. Child. 88:285 (Sept.) 1954.

2. Stokes, J., Jr., and others: The Carrier State in Viral Hepatitis, J. A. M. A. 154:1059 (March 27) 1954.

3. Neefe, J. R.; Norris, R. F.; Reinhold, J. G.; Mitchell, C. B., and Howell, D. S.: Carriers of Hepatitis Virus in the Blood and Viral Hepatitis in Whole Blood Recipients: I. Studies on Donors Suspected as Carriers of Hepatitis Virus and as Sources of Post-Transfusion Viral Hepatitis, J. A. M. A. 154:1066 (March 27) 1954.

4. Stokes, J., Jr.; Wolman, I. J.; Blanchard, M. C., and Farquhar, J. D.: Viral Hepatitis in the Newborn: Clinical Features, Epidemiology, and Pathology, A. M. A. Am. J. Dis. Child. 82:213 (Aug.) 1951.

5. Scott, R. B.; Wilkins, W., and Kessler, A.: Viral Hepatitis in Early Infancy, Pediatrics 12: 447 (May) 1954.

6. Krainin, P., and Lapan, B.: Neonatal Hepatitis in Siblings: Report of 2 Cases with Giant Multinucleated Liver Cells and Fatal Termination, J. A. M. A. 160:937 (March 17) 1956.

Large Ovarian Cyst in a Newborn Infant

Successful Removal

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Cysts of the ovaries are not common prior to puberty.[1] Schaefer et al. found only 6 cases of ovarian tumors in children in a series of more than 10,000 gynecological admissions to Queens General Hospital in New York.[2] These tumors are very rare before the age of one year.[3] Graves was able to uncover only 16 cystic and 2 solid ovarian tumors in infants less than 12 months of age.[3] Eight of these growths were probably present before birth, and two were of sufficient size to make delivery of the fetus difficult.

Ovarian tumors constitute approximately 1% of all tumors in children, according to Costin and Kennedy, who reviewed over 200 such cases.[4] One-third of these are simple or multilocular cysts; one-fourth, dermoid cysts, and one-third, carcinomas or sarcomas. Bilateral carcinoma of the ovaries in a 7-month stillborn fetus was reported by Ziegler.[5] In another series of 22 cases seen at the Mayo Clinic, 45% were dermoid tumors or teratomas.[4]

The clinical findings in an ovarian tumor can be varied. The size of the tumor may be sufficient to cause noticeable enlargement of the abdomen.[3,6,7,9] The most frequent symptom is torsion of the pedicle, which produces pain.[1,2,4,8] This presenting symptom occurred in 71% of the Mayo Clinic Series.[4] Proane found 4 cases of twisted ovarian cysts in 4514 surgical cases, the patients ranging in age from 6 months to 11 years.[8] Rarely the tumor may manifest itself by signs of precocious puberty.[2]

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The surgical removal of ovarian cysts in newborn infants has been infrequently reported.[3,6,7,9] The purpose of this paper is to report the successful removal of a very large ovarian cyst 48 hours after delivery.

Report of Case

A Negro girl was admitted to this hospital on May 8, 1956, approximately six hours after a normal delivery in another hospital. The infant weighed 7 lb. 8½ oz. and measured 19¼ in. in length. The only noticeable abnormality was marked generalized distention of the abdomen. The mother had received some antisyphilitic therapy during the last trimester of pregnancy. The infant's serologic test was positive. Paren-

Fig. 1.—Anteroposterior film demonstrates the large opaque mass filling all of the lower abdomen. The air-filled small bowel is displaced superiorly and to the left.

Fig. 2.—Lateral film. The mass is continuous with the pelvis. All the bowel is seen to be positioned superiorly and outlines the upper margin of the tumor.

teral penicillin was therefore administered. The abdomen contained a large mass which was thought to be cystic. X-ray examination revealed the intestinal gas pattern to be displaced upward and toward the left by a large area of homogeneous opacity suggesting fluid (Figs. 1 and 2). Suggested diagnoses were ovarian cyst, mesenteric cyst, urachal cyst, duplication of the gastrointestinal tract, and retroperitoneal tumor.

Because the infant was taking feedings very poorly, laparotomy was performed by one of us (D. G.) 48 hours after delivery. Ether anesthesia was used. The abdomen was entered through a transverse incision which divided both recti. A large simple cyst of the right ovary was easily delivered and removed. It was attached by a narrow pedicle. Abdominal exploration was otherwise negative. After surgery the infant took her feedings well. The operative wound appeared to be nicely healed when the infant was discharged from the hospital, on the 11th day after operation.

The cyst measured 13 cm. in diameter and weighed 490 gm. (Fig. 3). The pathologist reported it to be a corpus luteum cyst.

Summary

Cysts of the ovary in the newborn have been infrequently reported. The successful removal of a large simple cyst of the right ovary in an infant 48 hours after delivery is described.

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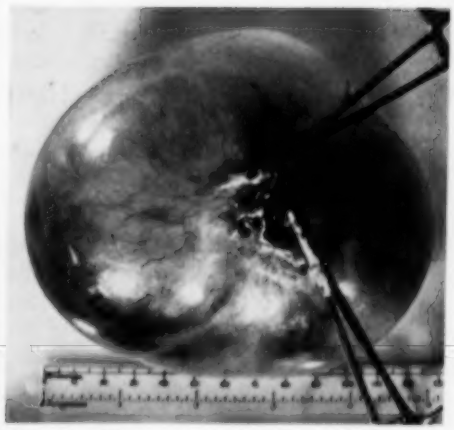

Fig. 3.—The surgical specimen, with hemostats at the pedicle site, with a centimeter ruler in the background. Tumor was 13 cm. in diameter.

REFERENCES

1. Ladd, W. E., and Gross, R. E.: Abdominal Surgery in Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, p. 389.

2. Schaefer, G.; Hills, F., and Veprovsky, E. C.: Ovarian Neoplasms in Children, Am. J. Obst. & Gynec. 58:718-726 (Oct.) 1949.

3. Graves, G. Y.; McIlvoy, D. B., Jr., and Hudson, G. W.: Ovarian Cyst in a Premature Infant, A. M. A. Am. J. Dis. Child. 81:256-258 (Feb.) 1951.

4. Costin, M. E., Jr., and Kennedy, R. L. J.: Ovarian Tumors in Infants and Children, Am. J. Dis. Child. 76:127-153 (Aug.) 1948.

5. Ziegler, E. E.: Bilateral Ovarian Carcinoma in a 30 Week Fetus, Arch. Path. 40:279-282 (Oct.) 1945.

6. Kunstadter, R. H.; Schultz, A., and Strauss, A. A.: Large Ovarian Cyst in a Newborn Infant, Am. J. Dis. Child. 80:993-998 (Dec.) 1950.

7. Neikirk, W. L., and Hudson, H. W., Jr.: Giant Ovarian Cyst in Newborn Infant, New England J. Med. 239:468-469 (Sept. 23) 1948.

8. Proane, C. A.: Cystic Torsion of Ovarian Pedicle in Infants and Children, J. Internat. Coll. Surgeons 16:724-730 (Dec.) 1951.

9. Bulfamonte, J. C.: Large Ovarian Cyst in Newborn Child, Am. J. Surg. 55:175-176 (Jan.) 1942.

Cysts of the Vagina in the Newborn Infant

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Congenital cysts of the vagina in the newborn infant are single cysts about ½ to ¾ in. in diameter located at the introitus of the vagina. They usually arise (Fig. 1) from the anterior wall and may extend on to the lateral wall. They are posterior to the urethra and anterior to the hymenal orifice and may give the appearance of a urethrocele.

Vaginal cysts of the newborn infant are said to be "not uncommon".[1] The accuracy of this statement is questionable, since most pediatric textbooks make no mention of the condition and experienced pediatricians and obstetricians have not seen a single case. Recently five newborn infants with cysts of the vagina were observed; three at Lebanon Hospital, one at Harlem Hospital (Fig. 2), and one at Jewish Memorial Hospital. All of them occurred in otherwise full-term normal infants. The pregnancy of each of the mothers of these children was normal and uneventful. In the child at the Jewish Memorial Hospital the cyst was larger than usual and obstructed the urethra. On the second day of life, because of urinary retention, operative removal was necessary.[11] In the child at Harlem Hospital there were no unusual symptoms, although a urethrocele was suspected. However, x-ray examination of the genitourinary tract with the aid of contrast medium revealed no abnormalities. The cyst emptied itself spontaneously and did not refill, and its presence could not be detected subsequently.

The following is a report of the three children at the Lebanon Hospital.

Case 1.—Newborn girl, product of normal, spontaneous, full-term delivery. Body weight 6 lb. 8 oz. On the second day of life a cyst the size of a hazelnut was noted on the anterior vaginal wall posterior to the urethral meatus. There appeared to be no interference with urination, and a catheter could easily be passed into the bladder. The hymenal orifice was patent. In view of the absence of symptoms, it was decided, after con-

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From the pediatric and obstetric services of Lebanon Hospital.

Fig. 1.—Vaginal cyst posterior to urethra, extending onto the lateral wall.

Fig. 2.—Vaginal cyst resembling a urethrocele.

sultation with Dr. H. Gordimer, that surgical removal could be postponed. Two days later the cyst ruptured spontaneously, and the child was discharged without further symptoms.

CASE 2.—Newborn girl, product of normal, spontaneous, full-term delivery. Birth weight 8 lb. On the third day of life a soft, pale, and cystic mass, about ¼ in. in diameter, was noted at the vaginal introitus. The mass was located on the anterior vaginal introitus. The mass was located on the anterior vaginal wall posterior to the urethral meatus (Fig. 2). As there appeared to be no obstruction, treatment was deemed unnecessary. The cyst ruptured spontaneously on about the 15th day of life and caused no further symptoms.

CASE 3.—Newborn girl, product of normal, spontaneous, full-term delivery. Birth weight, 7 lb. 10 oz. On the third day of life a fairly firm, pale, and cystic mass, approximately ½ in. in diameter was noted, arising from the right anterolateral wall of the vagina and displacing the hymenal orifice to the left. The urethral meatus was clearly visible anterior to the mass, and there was no difficulty in urination. The cyst was aspirated, and about 2 cc. of a milky white fluid was obtained. A Papanicolau smear was made, and this revealed squamous epithelial cells. A biopsy of the cyst revealed this to be lined by squamous epithelium.

Comment

Vaginal cysts in the newborn infant may arise from rests of the Wolffian or Müllerian ducts or may represent epithelial inclusions originating from the urogenital sinus.[2] Their difference in appearance can be understood by considering the embryology of the caudal end of the urogenital tract and the endocrine status prior to and immediately after birth.[9,7] The two sexes differ in the excretory pathways for the gametes; namely, in the male the mesonephric ducts (Wolffian ducts) form the vasa deferentia, while in the female these degenerate and usually disappear completely. Remnants of these ducts in the female are known as Gartner's ducts. These may become cystic or enlarged and in rare cases show malignant degeneration. Because of their origin, these cysts are lined by a flat or cuboidal epithelium.

The paramesonephric (Müllerian) ducts fuse at their caudal aspect to form the female genital tract. Aberrant remnants of these ducts may occasionally be found in the anterior wall.[2] The epithelium, being of the same type that gives rise to the vagina, is also under the influence of maternal hormones at the time of birth and is of the stratified squamous type. In this respect they cannot be differentiated from epithelial inclusions from the urogenital sinus.

Most reports of vaginal cysts are from the literature of other countries.[2-5,8,10] Potter,[6] in this country, illustrated one case and stated that the majority arise from remnants of the mesonephric duct. Meyer [4] reported that these cysts are present early in fetal life and can be readily traced to their respective parent structures.

A vaginal cyst may resemble a urethrocele and must be differentiated from it. Once the diagnosis is established the cyst may be removed, aspirated, or left alone. Surgical interference is indicated only when the cyst produces urethral or hymenal obstruction. None of the ruptured cysts have filled up again; nor can their former sites be identified.

Summary

Five newborn infants with cysts of the vagina have been seen. In one, because of urinary obstruction, operative intervention was necessary. Three cysts produced no symptoms and ruptured spontaneously. In the fifth case the pathological diagnosis was epidermal inclusion cyst filled with squamous epithelial cells.

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REFERENCES

1. Taussig, F. J.: The Female Reproductive System, in Brennemann's Practice of Pediatrics, edited by I. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1946, Vol. 3, Ch. 31, p. 24.

2. Vilas, E.: Cysten in der Scheide von Feten, Arch. Gynäk. 158:1-13, 1934.

3. Fevre, M., and Delon: Kystes vaginaux et urétrovaginaux chez l'enfant, Arch. franç. pédiat. 4:91-94, 1947.

4. Meyer, R.: Uber Cysten in der Vaginalwand von 3 Feten im Alter von 3 bis 5 Monaten, Arch. Gynäk. 151:576-586, 1932.

5. Mutel: Kyste du vagin chex un nouveau-né, Bull. Soc. obst. et gynéc. 23:452-453, 1934.

6. Potter, L.: Pathology of the Fetus and the Newborn, Chicago, The Year Book Publishers, Inc., 1952.

7. Paschkis, K. E.; Rakoff, A. E., and Cantarow, A.: Clinical Endocrinology, New York, Paul B. Hoeber, Inc., 1954.

8. Beier, W.: Gärtner'sche Gang Zysten der Scheide als Hinweiss auf weitere Missbildungen in Urogenitalsystem, Ztschr. Geburtsth. u. Gynäk. 143:71-86, 1955.

9. Hamilton, W. J.; Boyd, J. D., and Mossman, H. W.: Human Embryology, Ed. 2, Cambridge, England, W. Heffer & Sons, Ltd., 1952.

10. Wallis, O.: Multiple epithelcysten der Scheidenschleimhaut, Zentralbl. Gynäk. 57:1415-1420, 1935.

11. Bergman, H.: Personal communication to the authors.

Abstracts from Current Literature

Acta pædiatrica, Stockholm

46, No. 1 (Jan.) 1957

* C-Reactive Protein in Infancy. L. Philipson and E. Tveteras.—p. 1.
A Follow-Up Study of Children Treated for Acute Purulent Meningitis. C. G. Bergstrand, T. Fahlen, and A. Thilen.—p. 10.
Myalgia Cruris Epidemica. A. Lundberg.—p. 18.
Children Under Stress in Pediatric Clinic. W. C. Hulse, W. S. Davis, and H. Michal-Smith.—p. 32.
The Prophylaxis of Allergic Disease in Infancy and Childhood. J. Glaser.—p. 43.
Exocrine Gland Dysfunction in Cystic Fibrosis of the Pancreas. P. A. di Sant'Agnese.—p. 51.
Primary Tumor of the Heart. S. Edlund and K. Holmdahl.—p. 59.
Visceral Larva Migrans. R. V. Platou and P. C. Beaver.—p. 64.
Glycogen Content in the Placenta of Diabetic Mothers. F. Heijkenskjold and C. A. Gemzell.—p. 74.
Specific Desensitization in Bronchial Asthma in Childhood. I. Engstrom and S. Kraepelien.—p. 81.
Housing Conditions and Child Morbidity. V. Christensen.—p. 90.
Adolescent Mortality in The Netherlands. J. Braaksma-de Lint and J. H. de Haas.—p. 103.

C-Reactive Protein in Infancy.—This investigation was directed toward finding the answers to three questions: 1. What is the electrophoretic migration pattern of C-reactive protein? 2. Does CRP pass the placental barrier in significant amounts? 3. Does CRP production occur in appreciable titers in very young infants?

In an attempt to answer the first question, pooled CRP-positive serum was analyzed by a zone electrophoresis method in vertical columns with a cellulose medium, followed by tests for CRP in the relevant fractions. Results indicate that CRP is intermediate between γ- and β-globulins in its pattern of migration.

A second part of the investigation involved measurement of C-reactive-protein levels of women in the final states of pregnancy. Of 38 patients from the general obstetric wards 8 were found to have CRP levels none of which exceeded 2+, whereas in 6 of 16 cases from the infectious unit of the obstetric department significant levels of CRP were noted. Umbilical blood from 11 infants of these 14 patients with positive tests for CRP was examined, and in no instance was CRP demonstrated. It was concluded that this material does not pass the placental barrier.

Finally, 42 infants in the age range 0 to 6 months whose clinical condition was suggestive of the presence of CRP were tested, and of these 9 were positive; the youngest of these was one day old. These results were interpreted to indicate that the capacity to form C-reactive protein is present in early infancy.

A. M. A. Archives of Internal Medicine, Chicago

98:683-826 (Dec.) 1956

Tuberculous Pericarditis. David H. Spodick.—p. 737.
* Natural History of Glomerular Nephritis. Francis D. Murphy and Earl G. Schulz.—p. 783.
Nontropical Sprue. Manfred W. Comfort and Eric E. Wollaeger.—p. 807.

99:1-164 (Jan.) 1957

* An Intrafamilial Epidemic of Pharyngoconjunctival Fever. Robert G. Van Horne, Samuel Saslaw, George R. Anderson, Frederick J. Flatley, and Richard D. Carr.—p. 70.
* A Clinical Evaluation of the C-Reactive Protein Test. Richard S. Yocum and Alexander A. Doerner.—p. 74.
The Management of Acute Asthma. Haddon M. Carryer.—p. 82.
Thrombocytopenia Due to Infectious Mononucleosis. Albert V. Myatt and Richard H. Linn.—p. 139.

Natural History of Glomerular Nephritis.—The authors, who have had extensive experience with patients having various renal diseases, have reviewed the clinical course of 30 patients with chronic glomerular nephritis. These patients were studied from 10 to 34 years after the acute stage. Fifteen of the patients are dead; fourteen are living, and the final outcome in one patient is unknown. The authors feel that all cases of chronic glomerular

nephritis are the outcome of an acute phase which fails to heal completely, although often there is a failure to diagnose the acute phase because of a mild form. They feel that acute nephritis may take one of several courses: (*a*) heal completely; (*b*) die in the acute stage, or (*c*) pass into the transitional stage and become chronic. When nephritis has become chronic, it assumes a clinical course which is characterized by three stages: (*a*) transitional or latent stage; (*b*) degenerative phase, characterized by the nephrotic syndrome, and (*c*) terminal stage, characterized by azotemia.

The average duration of the transitional stage in the patients with chronic glomerular nephritis was 15.7 years. The hypertension usually made its appearance in the latter half of the transitional phase, and it was felt this was the most practical index that the disease was progressing. The development of hypertension was always considered as carrying a bad prognosis. The average duration of life after the development of hypertension in the group which died was 4.03 years.

Not all patients with chronic nephritis pass into the second stage—that of the nephrotic syndrome. Only 7 of the 30 patients in this series did so. The average duration of this nephrotic stage was 18 weeks.

The onset of the third stage of chronic nephritis is initiated by the appearance of azotemia. There is no recovery from this stage, which, in this series, lasted an average of 1.1 years. Cardiac complications were a frequent finding (70%) but were not the chief cause of death. Of the 15 patients who died with chronic nephritis, the cause of death in 7 was found to be uremia. In three patients the cause of death was a cardiovascular accident; in four patients death resulted from cardiac complications, and in one patient the cause of death was unknown.

Proteinuria was a persistent finding throughout the course of the disease in these patients who developed chronic glomerular nephritis and was the most reliable diagnostic sign. There was no demonstrable correlation between the amount of proteinuria and the outcome or duration of the disease.

Acute infections were found to cause an exacerbation of the nephritis. The female patients were evaluated to determine the course of their disease during pregnancy. Only 5 of the 13 female patients became pregnant after their chronic nephritis had become established. Two of these patients had uneventful pregnancies. One patient developed a nephrotic syndrome during the pregnancy. Another patient had a full-blown eclampsia which resulted in fetal death.

The authors feel that in all stages treatment should consist of adequate amounts of rest, a low-protein diet, and elimination of infection by use of antibiotics. During the nephrotic stage a low-salt diet must be maintained. In the nephrotic stage diuretics have been considered dangerous, and the authors do not favor the use of mercurial diuretics. Treatment with steroids is beneficial, but the use of these hormones at best only controls the edema. Whether the rigid use of these new steroids will alter the over-all prognosis can only be determined by a much longer period of observation. In the third and terminal stage, with azotemia, the fluid and electrolyte balances must be controlled, and one appears to be able to prolong life with the use of the newer antihypertensive drugs.

An Intrafamilial Epidemic of Pharyngoconjunctival Fever.—Pharyngoconjunctival fever has recently become recognized as a specific viral disease entity and is characterized by fever, pharyngitis, and conjunctivitis occurring either singly or in combination. Virus isolation studies have shown that the APC Type 3 virus is the etiologic agent. The authors describe a familial epidemic. APC Type 3 virus was isolated from three of seven persons with the acute illness. A significant rise in serologic titers occurred in four of the seven. The clinical symptoms in these four children with increased titers were strikingly similar in that all exhibited fever, conjunctivitis, pharyngitis, rhinitis, malaise, and cervical adenitis. Transient diarrhea was present in two of the four children. The incubation period was apparently between five to eight days as the disease progressed through the family. All patients responded to supportive therapy alone, without the use of antibiotics.

A Clinical Evaluation of the C-Reactive Protein Test.—The authors' experience with the C-Reactive Protein Test in 729 cases is reported. Any positive test is considered abnormal and should stimulate further investigative studies to determine the causative factor. The test, however, is certainly nonspecific and becomes positive in the acute phase of numerous abnormal conditions, such as trauma, infections, necrosis, neoplasms, and granuloma formations. In this series the test was consistently elevated in the sera of patients with bacterial infections, acute rheumatic fever, acute myocardial infarction, and widespread malignant processes. It was

commonly, but not consistently, found in cases of rheumatoid arthritis, virus infections, and active tuberculosis.

The test was rarely found to be positive in limited primary carcinoma with no clinical evidence of metastases.

The authors believe that this test is a more accurate indication of the presence of inflammatory necrotic processes than is the sedimentation rate.

American Heart Journal, St. Louis

53, No. 2 (Feb.) 1957

* Pulmonary Stenosis with Closed Ventricular Septum. M. Torner-Soler, J. M. Morató-Portell, and I. Balaguer-Vintró.—p. 213.

Paroxysmal Pseudoventricular Tachycardia and Pseudoventricular Fibrillation in Patients with Accelerated A-V Conduction. George R. Hermann, J. R. Oates, Thomas M. Runge, and Milton R. Hejtmancik.—p. 254.

The Nephrotic Syndrome. Arthur J. Merrill.—p. 305.

Pulmonary Stenosis with Closed Ventricular Septum.—The authors describe the clinical and laboratory features of valvular pulmonic stenosis with intact ventricular septum as demonstrated by a series of 15 patients ranging in age from 2 to 44 years. The diagnosis was proven in all cases by cardiac catheterization, angiocardiography, surgical intervention, or autopsy. In six of the cases there was an associated patent foramen ovale or auricular septal defect; in one there was a persistent left superior vena cava draining into the left auricle, and in one there was partial drainage of the pulmonary veins into the right auricle. In the remaining seven cases the only anomaly was the pulmonary stenosis.

Typical findings in these patients included a rough systolic murmur and thrill in the pulmonary area with a weak or absent pulmonary second sound. Cyanosis was present in eight of the cases. The authors point out that cyanosis may be central, owing to a right-to-left shunt, usually at the atrial level, or cyanosis may be peripheral, in association with congestive heart failure. Cyanosis is usually a relatively late manifestation, but if the stenosis is severe cyanosis may appear early; it was present within the first year of life in three of the cases reviewed.

It is noted that squatting and syncopal attacks are rare in this condition as opposed to their frequent occurrence in tetralogy of Fallot. Exercise tolerance was related to the degree of the pulmonic stenosis, and retardation of physical development was noted to occur in those cases in whom there was a venous-arterial shunt. Right-sided heart failure was a common occurrence in these cases.

Roentgen studies revealed various degrees of cardiac enlargement, a characteristic dilatation of the main pulmonary artery, and somewhat diminished vascular markings in the lung fields. Characteristic electrocardiographic tracings included evidence of right ventricular hypertrophy and, in addition, high-voltage P waves, seen especially in Lead II and interpreted as being due to right auricular strain.

The characteristic and diagnostic finding of pulmonic stenosis on cardiac catheterization was a marked pressure gradient across the pulmonary valve. In some instances catheter studies will reveal a left-to-right shunt at the auricular level, indicating the presence of a true auricular septal defect. With the ventricular septum intact, right ventricular systolic pressure may exceed systemic pressure, a condition which will not occur in tetralogy of Fallot. In the seven cases in which angiocardiograms were done the typical findings included demonstration of the poststenotic dilatation of the pulmonary artery with delayed evacuation of the right ventricle. In three of the cases in which there was a right-to-left shunt at the auricular level, early opacification of the left auricle and aorta was noted.

The authors point out that cases with mild pulmonic stenosis may not require surgery. They use as a guide for surgical selection the level of the right ventricular systolic pressure and believe that a level of 100 mm. Hg is an indication for surgical intervention.

American Review of Tuberculosis and Pulmonary Diseases, New York

75, No. 1 (Jan.) 1957

* Pulmonary Cysts: Five Cases with Preoperative and Postoperative Pulmonary Function Studies. Robert S. Meador and D. O. Shields.—p. 53.

Relationship of Isoniazid to the Metabolism of Mycobacteria: Catalase and Peroxidase. M. O. Tirunarayanan and W. A. Vischer.—p. 62.

Studies with C^{14} Labeled Para-Aminosalicylic Acid and Isoniazid. Alfred Heller, Robert H. Ebert, Dieter Koch-Weser, and Lloyd J. Roth.—p. 71.

75, No. 2 (Feb.) 1957

The Pathogenicity of Atypical Chromogenic Mycobacteria for the Rhesus Monkey. L. H. Schmidt, Richard Hoffmann, and William Steenken Jr.—p. 169.
Atypical Chromogenic Mycobacteria Associated with Pulmonary Disease. Emanuel Wolinsky, Marjorie M. Smith, Roger S. Mitchell, and William Steenken Jr.—p. 180.
A Limited Clinical, Pathologic, and Epidemiologic Study of Patients with Pulmonary Lesions Associated with Atypical Acid-Fast Bacilli in the Sputum. Horace E. Crow, Coleman T. King, C. Edwin Smith, Raymond F. Corpe, and Ingrid Stergus.—p. 199.
"Open Healing" of Tuberculous Cavities. Raymond F. Corpe and Ingrid Stergus.—p. 223.
The Course of Experimental Tuberculosis Inhibited by Isoniazid. Ben C. Sher, Z. George Czaja, Yosh Takimura, and Hans Popper.—p. 295.
* A Convenient Method for Measuring Ventilation: Based upon the Venturi Principle. Frederick C. Warring Jr. and Jan K. Siemsen.—p. 303.
Pulmonary Histiocytosis X. William Weiss and Dale Gordon Johnston.—p. 319.
A Case of Supernumerary Right Bronchus with Accessory Hypoplastic Lobe Containing a Bronchial Adenoma. Andreas D. Demetriades and Silik H. Polayes.—p. 326.
Rapid Detection of Drug-Resistant Tubercle Bacilli in Sputum by Slide Cultures. C. H. Pierce et al.—p. 331.
Chronic Bronchitis: Some Clinical, Pathologic, and Bacteriologic Aspects. N. Oswald.—p. 340.

75, No. 3 (March) 1957

* Pericardial Biopsy: Role in Diagnosis and Treatment of Chronic Pericarditis. Donald B. Effler and William L. Proudfit.—p. 469.
Studies on Isoniazid-Resistant Strains of Mycobacterium Tuberculosis: III. The Effect of Peroxide in Culture Media. Vincent C. Barry, Michael L. Conalty, Joan M. Denneny, and Frank Winder.—p. 476.
Pathogenic and Immunogenic Differentiation of Mycobacterium Tuberculosis Grown in Vitro and in Vivo. William Segal and Hubert Bloch.—p. 495.
The Significance of Delayed Emergence of Growth of Tubercle Bacilli. Edith L. Duerr.—p. 506.
Cycloserine Alone and in Combination with Other Drugs in Experimental Guinea Pig Tuberculosis. Emmanuel Wolinsky and William Steenken Jr.—p. 510.
Mode of Action of Isoniazid. John R. Maher, Joseph F. Speyer, and Morton Levine.—p. 517.
Viable and Stainable Counts of Tubercle Bacilli in Tuberculous Tissue. M. N. Affleck and D. F. Gray.—p. 519.

Pulmonary Cysts: Five Cases with Preoperative and Postoperative Pulmonary Function Studies.—In contrast to the management of a giant pulmonary bleb or bulla, it is often difficult to determine the proper management of symptomatic patients with a pulmonary cyst of moderate size. The authors report five patients of the latter type in whom ventilatory function of the lung was measured prooperatively and for a suitable period following operation. The condition of two patients was considerably improved, whereas in the three other patients the surgical procedure was not followed by improvement.

A Convenient Method for Measuring Ventilation: Based upon the Venturi Principle. Maximal breathing capacity has become accepted as the most useful and important of the dynamic tests of ventilation. It measures the integrated ability of the entire respiratory apparatus to perform maximal ventilation per unit time and is thus suitable for detection of restrictive and obstructive ventilatory deficiencies and of muscular fatigue.

The Venturi tube is a cylinder with an internal diameter which becomes progressively smaller from each end to the throat at the middle of the tube. The volume of air aspirated through the side arm of a modified Venturi tube (Ventube) can be related accurately to the volume of air passing to and fro through the throat of the tube. Calibration data and comparison with other methods show that this simple device is sufficiently accurate for the clinical measurement of maximal breathing capacity and exercise ventilation.

The Ventube is compact, portable, convenient to use, and easy to clean. Resistance to breathing through the tube is comparable to that encountered in low-resistance valves together with their connecting tubing.

Pericardial Biopsy: Role in Diagnosis and Treatment of Chronic Pericarditis.—Chronic pericarditis is an unusual condition, but it occurs more commonly than is generally believed. By tradition, pericarditis of undetermined etiology is suspected of being tuberculous in nature, and a presumptive diagnosis alone has often been the basis for treatment.

There is an appreciable risk in paracentesis for the diagnosis of pericardial effusion. Paracentesis in itself is a "blind procedure" and therefore has definite militations. Failure to obtain fluid does not prove it to be absent, nor does a sterile culture of a pericardial fluid necessarily exclude the presence of a specific organism within the pericardium. Pericardial biopsy, however, permits direct visualization within the pericardial sac; histopathologic examination and cultures of the diseased pericardium and fluid may establish the etiology of chronic pericarditis.

Twenty-two cases are reported. A technique of pericardial biopsy is described.

Bulletin of the Johns Hopkins Hospital, Baltimore

100, No. 2 (Feb.) 1957

The Development of Arterial Lesions Following Prolonged Sensitizations to Bovine Gamma Globulin. Frederick G. Germuth Jr. and R. H. Heptinstall.—p. 58.

Experimental Studies on the Immunologic and Histologic Effects of Prolonged Exposure to Antigen: I. Distribution of Allergic Lesions Following Multiple Injections of Bovine Albumin, Bovine Gamma Globulin and Albumin and Globulin Together with Special Reference to the Occurrence of Granulomatous Arteritis. R. H. Heptinstall and Frederick G. Germuth Jr.—p. 71.

Canadian Medical Association Journal, Montreal

76, Feb. 1, 1957

Polyarteritis Nodosa. N. G. B. McLetchie, R. M. MacDonald, and J. H. Cutts.—p. 213.

76, Feb. 15, 1957

* Staphylococcic Pneumonia in Infants and Young Children. J. N. Briggs.—p. 269.

* Galactosemia. H. W. Bain, D. H. Bowden, A. L. Chute, S. H. Jackson, A. Sass-Kortsak, and Norma Ford Walker.—p. 278.

Staphylococcic Pneumonia in Infants and Young Children.—This is a report of 27 cases of primary staphylococcic pneumonia seen at the Children's Hospital, Winnipeg, in 30 months. The presenting symptoms, mortality, complications, drug sensitivity, and culture results are discussed in detail and given in tabular form.

The mortality rate was high, 44%. The patients were all babies, only 5 of them being over 5 months of age, 16 being under 3 months. The commonest complications were collections of pleural fluid, empyema, atelectasis, and pyopneumothorax.

The author points out that Staphylococcus aureus is now an extremely common inhabitant of the nasal flora of all persons working in or associated with hospitals and assumes that resistant strains are becoming more prominent. He is alarmed at the fact that there are relatively few useful antibiotic agents left to combat the infection.

Galactosemia.—This is an excellent review article and must be read for an appreciation of the details of the disease. The authors emphasize that galactosemia is a congenital familial inborn error of metabolism characterized by malnutrition, hepatomegaly, galactose in the urine, and, at times, jaundice, cataracts, and mental retardation.

The purpose in presenting the paper is to suggest that the disease is commoner than has been suspected and is missed for the following reasons: (1) failure to obtain a urine specimen while the infant is on a milk feeding, (2) failure to consider the diagnosis in all dystrophic and marasmic infants, and (3) failure to consider the diagnosis in all atypical cases of jaundice in the newborn period.

In records of "biliary cirrhosis" in the Children's Hospital in Toronto there was definite evidence that some patients had had galactosemia but that it had been missed.

It is generally agreed that in these cases a specific gene necessary for proper galactose metabolism is absent or altered so that utilization of galactose is partially or completely impaired.

It is noted that all signs and symptoms, except perhaps cataracts and mental retardation, are reversed when milk products are removed from the diet.

Journal of the American Medical Association, Chicago

163, Feb. 16, 1957

Relation of Tonsillectomy and Adenoidectomy to Poliomyelitis. T. C. Galloway.—p. 519.

Surgery Versus Irradiation of Tonsils and Adenoids Relative to Conduction Deafness. S. H. Baron—p. 522.

Comparison of Surgical Removal of Tonsils and Adenoids with X-Ray Treatment. J. A. Weiss.—p. 526.

* Intersexuality. J. McC. Morris.—p. 538.

163, Feb. 23, 1957

Treatment of Undescended Testes. J. C. Kimbrough and J. F. Reed Jr.—p. 621.

Treatment of Cryptorchism. C. B. Drake.—p. 626.

Intersexuality.—The author gives the factors involved in sex determination and a classification of intersexuality. The correct diagnosis of intersexual problems may be difficult, but, because of the disastrous social and psychiatric consequences of an error in the diagnosis

of sex, careful evaluation is necessary. The following diagnostic procedures are thought helpful: (1) careful examination of the genitals, including a rectal examination (a photographic record may prove valuable); (2) an oral or vaginal cytological smear; (3) if the chromosomal pattern is female and congenital adrenal hyperplasia is suspected, 17-ketosteroid and pregnanediol level determinations usually suffice to establish the diagnosis; (4) urethroscopic examination and urethrograms may establish the fact that a urogenital sinus exists; (5) pyelograms; (6) surgical exploration with biopsy of gonads should be done as early as possible in practically all patients except those with congenital adrenal hyperplasia.

Journal of Pediatrics, St. Louis

50, No. 1 (Jan.) 1957

Vaccination with Avianized Smallpox Vaccine. M. Weichsel and E. G. Herrera.—p. 1.
Spontaneous Pneumothorax in the First 10 Days of Life. V. M. Howie and A. S. Weed.—p. 6.
Absorption of Acetylsulfisoxazole Lipid Emulsion. S. Krugman and F. Frieden.—p. 16.
The Use of Dermal Configurations in the Diagnosis of Mongolism. N. F. Walker.—p. 19.
Inkless Methods of Finger, Palm, and Sole Printing. N. F. Walker.—p. 27.
Congenital Choledochal Cysts. L. M. Horne.—p. 30.
Observations on the Clinical Use of V-Cillin in Pediatric Practice. M. Alvarez-Pagan, D. C. Rees, and G. F. Conway.—p. 39.
The Microspectrophotometric Determination of Blood Oxygen Saturation in Infants and Children. M. M. Pennoyer, M. R. Behrer, and M. G. Keso.—p. 44.
Alkaline Resistant (Fetal) Hemoglobin in Hypochromic Microcytic Anemias of Infancy and Childhood. I. L. Szeto, G. Asrow, and H. N. Sanford.—p. 49.
Jaw-Winking (Marcus Gunn Phenomenon). E. E. Smith and M. E. Gans.—p. 52.
The Value of Transillumination in the Diagnosis of Hydranencephaly. J. C. Levin.—p. 55.
Suprarenal Tumor (Cushing's Syndrome). M. G. Peterman.—p. 59.
Erythema Annulare Centrifugum (Darier) in a Newborn Infant. R. Fried, I. L. Schonberg, and J. Z. Litt.—p. 66.
Clinitest-Produced Esophageal Stricture. J. P. Canby.—p. 68.
Cor Triatrealum. G. M. Maxwell, W. P. Young, G. G. Rowe, and D. M. Connors.—p. 71.
* The Abnormal Hemoglobins: Clinical and Hematologic Aspects. C. H. Smith.—p. 91.
Human Salivary Gland Virus (SGV). R. J. Blattner.—p. 125.

50, No. 2 (Feb.) 1957

A Long-Term Evaluation of the Juvenile Diabetic. T. H. Joos and J. A. Johnston.—p. 133.
Intrathecal Hydrocortisone in the Treatment of Tuberculous Meningitis. C. Choremis, C. Papadatos, A. Gargoulas, and C. Dross.—p. 138.
* Nocardiosis in Childhood. C. N. Ballenger and D. Goldring.—p. 145.
The Effect of Corticotropin on the Activity of the Adrenal Cortex in the Male Child. S. P. Gottfried, M. Bogin, and N. V. Levycky.—p. 170.
A Study of Venous Pressure in the Newborn Infant. R. P. Parkinson.—p. 174.
Relationship Between Clinical Status and Behavior Test Performance in a Newborn Group with Histories Suggesting Anoxia. F. K. Graham, M. M. Pennoyer, B. M. Caldwell, M. Greenman, and A. F. Hartmann—p. 177.
Evaluation of Sulfaethylthiadiazole (SETD) in Common Infectious States in Children. J. D. Farquahar.—p. 190.
A Clinical Approach to Infantile Colic. Lawrence Breslow.—p. 196.
Wolff-Parkinson-White Syndrome. M. A. Jansa.—p. 207.
Classification and Etiological Factors in Mental Retardation. H. Yannet.—p. 226.
Role of Physician in Maintaining Continuity of Care and Guidance. R. W. Deisher.—p. 231.
Research in the Field of Mental Retardation. H. Yannet.—p. 236.
Varicella Pneumonia. R. J. Blattner.—p. 258.

50, No. 3 (March) 1957

The Urinary Excretion of Amino Acids and Sugars in Early Infancy. L. I. Woolf and A. P. Norman.—p. 271.
Loeffler's Pneumonia Associated with Hypogammaglobulinemia. C. Aziza and J. H. Lapin.—p. 296.
Pediatric Use of Dioctyl Sodium Sulfosuccinate. F. Tevetoglu.—p. 304.
Hereditary Spherocytosis in the Neonatal Period. C. M. Shapiro, A. M. Josephson, S. Rozengvaig, and A. Kauffmann.—p. 308.
Neonatal Hepatitis in Siblings. M. G. Peterman.—p. 315.
Hirschsprung's Disease in the Neonatal Period. D. H. Bowden, A. M. Goodfellow, and J. D. Munn.—p. 321.
Growth and Development of Negro Infants: VIII. Comparison of the Deciduous Dentition in Negro and White Infants. A. D. Ferguson, R. B. Scott, and H. Bakwin.—p. 327.
* Infantile Myoclonic Seizures. H. W. Baird and L. G. Borofsky.—p. 332.
Premature Infant Mortality. J. H. Corey, W. W. Waddell Jr., and F. N. Mitchell.—p. 340.
Agenesis of the Corpus Callosum. F. P. Koch and P. J. Doyle.—p. 345.
Purulent Neonatal Meningitis. D. G. Watson.—p. 352.

Iliac Vein Obstruction Caused by Retroperitoneal Abscess in Newborn Infants. E. Grunwaldt and E. J. Tomsovic.—p. 361.
Explosion of Nursing Bottles. P. J. Burnham.—p. 371.
The Responsibilities of the Medical Profession in the Use of X-Rays and Other Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation.—p. 372.
Chromogenic Acid-Fast Bacilli from Human Subjects. R. J. Blattner.—p. 385.

50, No. 4 (April) 1957

The Community Responsibility for the Care of the Mentally Retarded. H. Yannet.—p. 397.
Brazilian Experience with Oral B. C. G. E. Budiansky.—p. 404.
Subacute Sclerosing Leukoencephalitis. C. M. Poser and J. Radermecker.—p. 408.
* Laboratory and Clinical Studies on Candidiasis in the Newborn Infant. C. L. Taschdjian and P. J. Kozinn.—p. 426.
The Utility of Blood Exygenation as an Indicator of Postnatal Condition. B. M. Caldwell, F. K. Graham, M. M. Pennoyer, C. B. Ernhart, and A. F. Hartmann.—p. 434.
Hereditary Spherocytosis in Infancy. G. C. Robinson and J. M. McKenty.—p. 446.
Hereditary Cerebral Palsy. Johanna Blumel, E. B. Evans, and G. W. N. Eggers.—p. 454.
The Chloride Concentration of Saliva and Sweat in Infancy. J. Dancis, E. Grobow, and A. Boyer.—p. 459.
Hyperkinetic Behavior Syndrome in Children. M. W. Laufer and E. Denhoff.—p. 463.
Agammaglobulinemia. E. Freundlich.—p. 475.
Cutaneous Moniliasis in a Premature Infant. W. H. Cabaniss, W. F. Manley, and R. E. Swan.—p. 480.
Pulmonary Moniliasis. P. S. Sahni.—p. 484.
Infantile Cortical Hyperostosis. M. F. Morrison.—p. 487.
Poisonous Plants. W. H. Wood.—p. 499.
Serious Complications of Varicella Including Fatalities. R. J. Blattner.—p. 515.

The Abnormal Hemoglobins: Clinical and Hematologic Aspects.—The author summarizes the essential features of the principal clinical states and hematological aspects. The hemoglobin types are determined by two methods: (1) the detection of fetal hemoglobin by the method of alkali denaturation and (2) the separation of the abnormal hemoglobins by paper electrophoresis. The various hemoglobins reported and their differentiation by paper electrophoresis are as follows: The most rapid moving are H and I, which move the same at pH 8.6 but can be separated at pH 6.5; next comes J; then comes A; F comes next but is usually poorly separated from A; G has same mobility as F, but G is not alkali-resistant; then come S and D, which have same mobility but can be separated by the fact that D is much more soluble in the reduced form than is S when reduced; then comes E, and the slowest is C; a new hemoglobin, designated as P, has recently been described, and its mobility is slower than A and F. A is adult hemoglobin; F is fetal, and S is sickle-cell. Hemoglobins C and E are well established as causes of disease. Hemoglobin P is normally found in the fetus during the first half of embryonic life and is then replaced by F. It is said to be found postnatally in severe hypoproteinemia and in agammaglobulinemia, but not much work has been done on it.

In the inheritance of these diseases it has been demonstrated that with few exceptions hemoglobins S, C, D, and E represent alleles of normal hemoglobin A. Apparently the gene for thalassemia is different from the one for the hemoglobins. The author also points out that the amount of hemoglobin in a blood sample is influenced by interaction with the gene controlling another type of hemoglobin with which it is combined. Thus, in the combination of a gene for thalassemia and for sickle cell the amount of sickle-cell hemoglobin may be as high as 80%, whereas it is lower than 50% in the parent.

Fetal hemoglobin comprises 44% to 89% of the hemoglobin in the newborn and decreases rapidly. After 30 months of age 2% is the upper limit. It is found in excess in thalassemia, sickle-cell anemia, and, occasionally, in chronic congenital aregenerative anemia, acute and chronic leukemia, and metastatic carcinoma involving the bone marrow and also in some cases of congenital spherocytic anemia.

The accompanying Table gives the characteristics of the various hemoglobinopathies. As far as the other hemoglobins are concerned, the following information is available: Homozygous hemoglobin D has not been reported, and the trait is identified only by electrophoresis; homozygous hemoglobin G (one case) is asymptomatic, as is the trait; hemoglobin G-sickle cell resembles sickle cell-thalassemia; hemoglobin G-thalassemia is a little more severe than thalassemia minor; hemoglobin H found in three members of a Chinese family was associated with a condition resembling thalassemia in which there were also intraerythrocytic inclusion bodies; hemoglobin I is associated with no abnormalities; hemoglobin J was found in heterozygous form and had no accompanying abnormalities.

Characteristics of Hemoglobinopathies

Disease	Race	Anemia	C. V. *	Iron Content	O. F. *	Sickling	Target Cells	Bone Marrow	Hb. Present	Arthralgia	Splenomegaly	Hepatomegaly	Abd. Pain	Miscellaneous
Sickle-cell trait	Negro	No	N	Normal	N	Yes	Few	Normal	S, 24%–45%; A, rest	Rare	No	No	Rare	Resist. to malaria; intravascular hemolysis at high alt.
Sickle-cell anemia	Negro	Yes 6–8 gm.	N	Normal	D	Yes 100%	Inc.	Hyperactive	S, 60%–98%; F, rest	Yes	Yes	Uncommon	Yes	Aplastic crises
Thalassemia minor	Medit. groups esp.	Mild	M. C.	Hypochromic	D	No	Prominent	Slightly Hyperactive	A	Uncommon	Slight	No	No	
Thalassemia major	Medit. groups esp.	Yes	M. C.	Hypochromic	D	No	Prom. up to 10%	Hyperactive	F, 40%–100%; A, rest		Marked	Marked	Occ.	Inability to synthesize A in normal amounts
Homozygous C	Negro	Mild	N	Normal	D	No	Marked (40–90%)	Hyperactive	C, 100% C, 28%–44%;	Uncommon	Marked ?		Uncommon	
Hb. C trait	Negro	No	N	Normal		No	Numerous		A, rest	No	Slight			
Homozygous E	Thia	Mild	M. C.	Hypochromic	D	No	Numer. (25–60%)	Hyperactive	E, 94%–98%; F, rest	Mild	Slight	Slight		
Hb. E trait	Thia.	No	N	Normal	N	No	No	Normal	E; A, F, 2%	No	No	No		
Sickle-cell thalassemia	White & Negro	Mod. 6–9 gm.	M. C.	Hypochromic	D	Yes	Numerous	Hyperactive	S, 65%–90%; A, rest (occ. F)	Yes	Mod.	May be marked	Yes	
Sickle-cell Hb. C	Negro	Usually mild 9–10 gm.	N	Normal	?D	Yes	Numer. (aver. 60%)	Hyperactive	C & S, about equal; F, up to 7%	Yes	Yes	Yes	Yes	Pregnancy carries more risk than in homozygous S
Sickle-cell Hb. D	White	Mild 8–10 gm.	N or M. C.	Normal		Yes	Rare	Hyperactive	C & D, about equal; F, up to 12%		May be marked	May be marked		
Thalassemia Hb. C	Negro	Usually Mild	M. C.	Hypochromic	N or D	No	20–60%	Hyperactive	C, 65%–90%; A		Mod.	Mod.		
Thalassemia Hb. E		Severe	M. C.	Hypochromic	D	No	5–10%	Hyperactive	E, 60%–80%; F, rest	Yes	Massive	Mod.	Yes	Splenectomy may promote growth

* C.V., cell volume; O.F. osmotic fragility; N, normal; D, decreased; M.C., microcytic.

Nocardiosis in Childhood.—The author reports a case of nocardiosis and reviews the literature. The child was about 3 years old at death, but his symptoms started at age 7 months. His course was chiefly that of a chronic progressive pulmonary disease with generalized lymphadenopathy, hepatosplenomegaly, chronic leukocytosis, anemia, and growth failure. Innumerable studies were carried out. Fibrocystic disease was ruled out; agammaglobulinemia was ruled out; innumerable cultures of all kinds were negative, as were skin tests and serological tests. At one time the sulfonamides seemed to be helpful. At autopsy the left lung was practically replaced by yellow friable suppurative tissue; the right lung showed a nodular yellowish consolidation; the spleen, kidneys, liver, and thyroid were extensively involved. Smears of the pus revealed Gram-positive, non-acid-fast, branching filamentous organisms. The culture was positive for Nocardia asteroides.

The author found 95 cases reported in the world literature, most of which were diagnosed at autopsy or soon before death. The lungs were involved in two-thirds of the cases, with the brain and subcutaneous tissues next. A total of 65 cases died; 20 recovered, and 10 are unknown. The organisms appear in smears of pus, as noted above; they may be weakly acid-fast; they fragment into bacillary and coccal forms, the former of which may be indistinguishable from tubercle bacilli; they are destroyed when gastric washings are concentrated for tubercle culture. The organism is closely related to the tubercle bacillus and to the anaerobic actinomycetes. Agglutinins, complement-fixing antibodies, and precipitins have not been demonstrated in man, although they are found in experimental infection; however, positive skin tests have been shown in man.

The clinical features of the disease are more often those of acute and chronic pulmonary disease; they may be those of chronic suppurative disease of the skin, subcutaneous tissues, and bone; that of a primary disease of the central nervous system, or that of a widely disseminated infection with multiple-system involvement. The diagnosis is based on the recovery of the organisms from blood, sputum, or exudates. It is sensitive to many antibiotics in vitro, and this may interfere with cultures. The survival rate seems related to the early bacteriological diagnosis. The drug of choice is sulfadiazine. Surgical drainage should be used when possible. A high index of suspicion and repeated cultures are the most promising methods of making the diagnosis.

Infantile Myoclonic Seizures.—The authors review their experience with infantile myoclonic seizures because of the observation that a number of these patients had normal histories prior to their immunization with diphtheria, pertussis, and tetanus antigens.

The syndrome of infantile myoclonic seizures is generally recognized as having a poor prognosis for future mental development. Often they progress slowly from birth, but some patients do well for five or six months and then start to show failure in speech and other interpersonal relationships even if motor development is good. These seizures may be the clinical manifestation of a severe cerebral malformation or of a variety of pre-, para-, or postnatal insults to an immature brain. Hypsarhythmias, though found sometimes in children with other types of convulsions or with other types of involvement of the central nervous system, are almost always present in infantile myoclonic seizures. Hypsarhythmia is defined as a 1- to 2-per-second spike and wave pattern of high voltage prominent in all leads.

Out of 2000 electroencephalograms 80 children showed hypsarhythmia. Of these, 71 had a history of one or more convulsions—17 only grand mal, 1 grand mal and simple staring petit mal, 2 one-sided tonic and clonic seizures, 51 myoclonic seizures alone or combined with other types. The 51 are considered in the rest of the report. Motor development: Twenty-four had normal motor development in early infancy.

Age at onset: There were 44 whose seizures started before first birthday; remaining 7, before 18 months.

Mental retardation: Forty-three had developmental quotient less than 50% by Gesell standards; the remaining eight were much worse (of the twenty-nine who had hypsarhythmia on EEG but another type of convulsion or no convulsion and did not have myoclonic seizures, only one had a normal I. Q.).

Association with cerebral palsy: There were 16 with a demonstrable motor defect of central origin (quadriplegia 7, hemiplegia 6, diplegia 2, atonic diplegia 1).

Eye involvement: There were 11 with marked visual problems (blind 4, strabismus 2, cataracts 1, optic atrophy 4).

Etiological factors—two groups: (*a*) There were 27 retarded from birth (3 hereditary, 1 congenital toxoplasmosis, 7 maternal illness during pregnancy, 7 with difficult delivery, 9 no

contributory histories); (*b*) 24 developed normally from time of birth; possible factors were vaccination for smallpox in 2, encephalitis of unknown cause in 2, chicken pox encephalitis in 1, measles encephalitis in 1, tuberculous meningitis in 2, pertussis encephalitis in 1, head trauma with subdural hematomas in 2, DPT immunizations in 9.

Therapy: Seizures spontaneously disappear before 5 years of age. All sorts of therapy were tried, usually with poor success. Perhaps phenobarbital, meprobamate (Miltown), and ketogenic diet were most effective.

The authors describe the infantile myoclonic seizure. In some it is a sudden dropping of the head with adduction and flexion of the arms. In others there may be a sudden lightning-like contraction of the flexor muscles of the trunk accompanied by abrupt flexion of arms on the chest and thighs on the trunk. It may resemble sudden attacks of colic. The authors feel that DPT immunization may be responsible for some cases, just as other types of neurological manifestations may follow DPT immunization, and just as other types of encephalitis may cause myoclonic seizures.

Because developmental achievements are based on memory, they are subject to error. The authors make a plea for examinations of babies to include such things as (1) ability to raise head momentarily from prone position (present from birth on); (2) evidence that control of head, neck, and back is adequate for age; (3) cooing, vocalizing, socializing before 3 months of age; (4) ability to relate to parents and examiner; (5) general interest in environment.

Laboratory and Clinical Studies on Candidiasis in the Newborn Infant.—This study was undertaken to evaluate the occurrence and significance of Candida albicans in the mouth and intestines of newborn infants. Previous studies had been contradictory; Epstein had found that only 50% of infants who harbored the organism developed clinical thrush; on the other hand, Anderson and others reported that 100% developed clinical disease.

The authors took at least two oral swabs and cultures from 2175 newborn infants in the first week of life. They also took 520 stool cultures on third, fourth, and fifth days of life. Recognized bacteriological techniques were used to identify organisms.

Of the 2175 infants, 82 were found to harbor C. albicans (3.77%). Of these, 67 were positive from the third day onward; 66 of the 82 developed oral thrush within one to five days of the first positive smear. One with a positive smear developed cutaneous moniliasis but no oral thrush (diaper area). Of 15 with positive cultures but negative smears, 7 were lost from observation and 6 of the remaining 8 had cutaneous moniliasis, the other two remaining clinically negative. In evaluating the smears, it was found that preclinically only extracellular blastospores were present; when blastospores were found intracellularly and hyphae were present, clinical thrush was evident within 12 hours. Also, if only scant blastospores were present and extracellular thrush did not occur or was delayed in its appearance; several of these infants did develop cutaneous moniliasis. In their series of newborns, about 98.5% of those with positive smears or cultures developed clinical lesions.

Concerning the intestinal tract, the authors found 52 infants with positive stool cultures, 5 of whom were lost from observation. Of the 47 remaining, 11 had oral thrush only, 23 had oral and cutaneous, 12 had cutaneous only, and one had no clinical manifestations. The cutaneous lesions were usually in the diaper area.

The authors feel that their study leads to the conclusion that one should routinely smear and culture the newborn's mouth on the fourth day. If the culture is positive for C. albicans, treatment should be instituted, preferably oral therapy in order to rid the intestinal tract of the organism also and thereby reduce the incidence of cutaneous moniliasis.

Medizinische Klinik, Munich

51, No. 51, 1956

The Clinically Separate Position of Rheumatism in Children. E. Stoeber.—p. 2153.
* Intoxications with Insecticidal Phosphoric Acid Esters. I. Krause and E. Otters.—p. 216.

51, No. 52, 1956

Clinic and Therapy of Primary Chronic Polyarthritis in Childhood. E. Stoeber and G. Kölle.—p. 2197.
Sedaraupin (Reserpine) Therapy in Children with Cerebral Injury. I. Wallis.—p. 2221.

52, No. 4, 1957

Prophylaxis of Focal Infection in Childhood. F. Thoenes.—p. 121.
Piperazine Intoxication on Therapeutic Dosage. D. Greuel.—p. 129.
Symptomatology and Therapy of Virus-Hepatitis and the "Dyshépatie lipidogéne" in childhood. W. Karpinski —p. 131.

Intoxications with Insecticidal Phosphoric Acid Esters.—The thiophosphoric acid ester Metasystox was taken by a mother and two children, 2 and 4 years of age. Its toxicity and anticholinesterase activity are less than those of other related insecticides used for plant protection. The prominent symptoms were an intensive odor, maximal miosis, and much salivation. Atropine was injected intravenously 0.15 mg. immediately, later subcutaneously, until the pupils dilated. This happened after the administration of about 3 mg. Stomach gavage was employed, medical charcoal and a saline cathartic were administered. Recovery was complete in a week.

Piperazine Intoxication on Therapeutic Dosage.—Piperazine (Diaethylendiamine) is an anthelmintic. It has been regarded as well tolerated by children in a dosage of 150 mg. per kilogram. A 4½-year-old boy received 138 mg. per kilogram of piperazine citrate for four days. While taking the medication he suffered abdominal pain and vomited. The next day he was insecure on his feet. With cessation of medication and bedrest he recovered. About two weeks later the treatment was repeated, with the same dosage. On the third day he again had abdominal pain and nausea, insecurity in walking, and muscular weakness of the legs. The symptoms disappeared within 48 hours after cessation of medication. The family physician reported that a 3-year-old brother reacted in the same manner to piperazine citrate. The desirability of determination of the therapeutic minimal dose is stressed.

Minerva pediatrica, Turin

9, Feb. 17, 1957

' The Carbohydrate Metabolism of the Newborn: I. and II. The Effects of the Somatotropic Hormone (STH) and of Glucagon on Hypoglycemia in the Newborn Premature Infant. R. Bulgarelli and L. Tognoni.—p. 145.
A Clinical Study with a Type of Humanized Milk (S. M. A.) P. Nicola.—p. 165.
The Antistreptolysin Titer in the Newborn. E. Arditi and N. Nigro.—p. 170.
A Case of Embryonic Adenoma of the Thyroid in a 9-Year-Old Girl. W. Tangeroni and L. Pardelli.—p. 173.

9, Feb. 24, 1957

' Purulent Meningitis in the Newborn. A Verga and G. Cipollone.—p. 185.
Two Cases of Spontaneous Pneumothorax in the Newborn. G. Bracco and M. T. Gandolfo Caramello.—p. 200.
A Case of Systemic Reticuloendotheliosis (Histiocytosis X): The Effects of Treatment with 6-Mercaptopurine, Prednisone, and Roentgen Therapy. G. Conca and A. Mazza.—p. 203.
' Undersized Children and Adolescents: The Hereditary and Non-Hereditary Types; A Study of 200 Cases. E. Comolli.—p. 212.

The Carbohydrate Metabolism of the Newborn.—A review of the literature as to blood sugar findings in newborn infants is given; similar reported data on premature infants have been much less in amount and consistency.

In this study, the blood sugar findings in 25 premature infants varied from 49 mg. to 95 mg. per 100 cc. (mean, 72 mg.); any variations did not appear to be related to the body temperature, weight, or height. The injection of the somatotropic hormone (50 U. E.) resulted in an average increase of the blood sugar of 25 mg. per 100 cc.; in three of the cases the increase was much smaller, and in one case, not present. When glucagon (0.2 or 0.4 mg. per kilogram) was injected into five premature infants, the blood sugar showed an average increase of 32 mg. per 100 cc.

The conclusion is drawn that the pituitary hormone (STH) will cause a much greater, and the pancreatic hormone (glucagon) a much less, rise in the blood sugar levels of premature infants than of children or of adults.

Purulent Meningitis in the Newborn.—Reports are presented of 15 cases of purulent meningitis in newborn infants. Only 2 of the infants have shown complete recovery; 1 has developed hydrocephalus, and 12 have died. Four of the infants were premature; all of them died. The causative organisms were pneumococci in three, with one recovery; Staphylococcus aureus in three, with one recovery; Hemophilus influenzae in 2; B. coli in

one, and Meningococcus and B. coli in one. The percentage of recoveries was about the same as has been reported by others. Contributing factors as to the etiology in meningitis of the newborn include obstetrical and maternal conditions, as eclampsia, cesarean section, forceps, anoxia, hemorrhage; malformations, as spina bifida, and umbilical infection. The high percentage of fatalities must in part be attributed to a late diagnosis, as the symptoms of meningitis in the newborn are often obscure and easily missed by the attending physician.

Undersized Children and Adolescents: The Hereditary and Non-Hereditary Types; A Study of 200 Cases.—Data and measurements are presented for 107 boys and girls, whose small size was apparently on an hereditary basis (Group I). Similar data were obtained for 93 children whose small size was apparently not attributable to hereditary factors (Group II).

In Group I, one-third of the children were proportionally small for their ages in both height and weight; the other two-thirds were more subnormal in height than in weight; the bone age was usually normal, but the dental age tended to be retarded; about one-fifth of the children showed slight subnormal sexual development; their intelligence was superior in 4, normal in 63, low normal in 19, and deficient in 8 of the children examined; both of the parents were of normal stature in 12 cases, while in 88 one or both of the parents were of subnormal stature.

In Group II, the children were more frequently more subnormal in weight than in height and were more frequently retarded in bone age than in dental development; 47% of the children were subnormally developed sexually; 1 child was of superior, 29 of normal, and 23 of low normal intelligence, while 34 were mentally deficient; the parents were both of normal height in 29 cases, while one or both parents were of subnormal height in 45 cases.

Monatsschrift für Kinderheilkunde, Berlin

104:403-438 (Oct.) 1956

Dye-Test Studies for Toxoplasmosis in Children. J. Paul.—p. 403.
* The Clinical Significance of the Cisterna Interventricularis. Hans Schoenenberg and Oskar Wolff.—p. 410.
Normal Values for Unipolar Leads in the Electrocardiogram of Children. Joachim Stoermer.—p. 415.
* Etiological and Epidemiological Role of Pseudomonas Pyocyaneus in Diarrhea of Premature Infants. L. Gyergyai, T. Bodo, L. Toth, and H. Kelemer.—p. 420.
Epiglottitis Phlegmonosa Oedematicus Acutissima. H. G. Arlt.—p. 424.
Review Article: Acute Infectious Diseases. F. Hansen.—p. 426.

104:439-474 (Nov.) 1956

* Blood Bile Acid Levels in Pediatrics. Gerhard Joppich.—p. 439.
Possibilities and Dangers of Rickets Prophylaxis and Comparative Experiments with Vitamin D Irradiated Milk. W. Theopold and Inge Schulte-Nickell.—p. 442.
* The Clinical Significance of the Hemagglutination Reaction for Tuberculosis in Pediatrics. J. Toeroek.—p. 447.
A Method for Spot Bronchography in Young Children. Heinz Schmidt-Rohr.—p. 457.
Otitis Media in Children. Saara Heikkilae and Thomas Peltonen.—p. 463.
Report of the Eighth Annual International Congress of Pediatrics.—p. 468.

The Clinical Significance of the Cisterna Interventricularis.—Pneumoencephalography was performed in 50 children, mostly infants and young children with mental retardation and convulsions. It was possible to visualize the cisterna interventricularis in these patients. It was also possible to visualize it in a few older children, in children without mental retardation, in two children with myotonia congenita, two with Sturge-Weber syndrome, and one each with chondrodystrophy, arthrogryposis multiplex, nystagmus, dysostosis multiplex and incontinentia pigmenti. In two cases the cisterna interventricularis was demonstrated at autopsy.

Visualization of the cisterna interventricularis can be considered as proof of brain malformation.

Etiological and Epidemiological Role of Pseudomonas Pyocyaneus in Diarrhea of Premature Infants.—In vitro studies showed that oxytetracycline (Terramycin) alone or in combination with streptomycin was the most effective agent against Pseudomonas pyocyaneus. Chloramphenicol (Chloromycetin) in high concentrations (25γ to 50γ per milliliter) was effective against Proteus vulgaris. Combination with other antibiotics did not produce synergism.

Sensitivity studies are indispensable in ascertaining the most effective antibiotic or combination of antibiotics in severe infections, especially diarrheal outbreaks.

Blood Bile Acid Levels in Pediatrics.—With use of the method of Koransky and Thiele 132 blood bile acid determinations were performed on 117 patients. Adults without liver disease showed values between 2.7 and 3.5 mg. per 100 cc.; children without liver disease showed values between 2.4 and 4.1 mg. per 100 cc.

During the course of acute hepatitis values rose to two to four times above normal but returned to normal rapidly. No increase was noted with anicteric hepatitis. Failure of blood bile acids to fall after hepatitis spoke for cirrhosis. This was usually characterized by increased blood bile acid levels. This was also observed in patients with obstructive jaundice. It was impossible to make a differential diagnosis between parenchymatous and obstructive jaundice on the basis of blood bile acid levels. Icterus neonatorum and icterus gravis usually showed increased blood bile acid levels. This was also found in patients with renal disease, obesity, in one patient with Nieman-Pick disease, and in one with typhus, despite lack of detectable liver disease. In these instances extrahepatic influences upon bile acids, which are, after all, lipids, was postulated.

Therefore, it could be stated that liver disease constituted the most important but not the only cause for increased blood bile acid levels.

The Clinical Significance of the Hemagglutination Reaction for Tuberculosis in Pediatrics.—Between 1951 and 1954 more than 4000 Middlebrook-Dubos hemagglutination tests for tuberculosis (modified by Foëldes and Koeroesi) were performed on children in a Hungarian University Clinic and Hospital.

In 12.8% of nontuberculous children borderline positive and positive titers were obtained. In 50.3% of children with tuberculosis negative reactions were found. With increase in age and increase in the number of positive tests among nontuberculous children as well as among children with negative tuberculin tests was found. Young infants with tuberculosis generally had negative hemagglutination titers.

Neither diagnostic nor prognostic conclusions could be reached on the basis of height of titers with use of serial determinations in infants and children with tuberculous meningitis. This also held true when agglutination tests were performed on cerebrospinal fluid.

Following vaccination with BCG hemagglutination titers sometimes became temporarily positive but they did not remain elevated for longer periods of time. There was no correlation between hemagglutination titers and tuberculin sensitivity. There was no change in the titer of patients with tuberculous meningitis after their tuberculin sensitivity had disappeared.

Umbilical cord blood of infants born to tuberculous mothers usually did not contain agglutinins; in rare instances there were titers comparable to those in the mothers.

On the basis of these observations it was concluded that the hemagglutination reaction for tuberculosis has only theoretical significance at this time. Only after more specific and sensitive methods have been perfected can it be used for systematic clinical purposes.

New England Journal of Medicine, Boston

255, No. 18 (Nov. 1) 1956

Dermatologic Therapy of Yesterday and Today. A. Hollander.—p. 833.
Exacerbation of Pre-Existing Neurologic Disease After Spinal Anesthesia. L. D. Vandam and R. D. Dripps.—p. 843.
Acute Encephalitis with Intranuclear Cellular Inclusions: A Nonfatal Case of Probable Herpetic Etiology Diagnosed by Biopsy. P. R. Dodge and C. W. Cure.—p. 849.
Proctology. E. P. Hayden.—p. 854.
A Consideration of Childbirth Programs. H. Thoms and W. C. Billings.—p. 860.

255, No. 19 (Nov. 8) 1956

* Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus Group B, Type 3. S. Kibrick and K. Benirschke.—p. 883.
Some Observations on the Incidence of Thyroid Cancer in the United States. P. Mustacchi and S. J. Cutler.—p. 889.
Hypertensive Vascular Disease in Adolescence. R. P. Masland Jr., F. P. Heald, W. T. Goodale, and J. R. Gallagher.—p. 894.
Plastic Surgery: Tissue and Organ Homotransplantation. B. Cannon and J. E. Murray.—p. 900.
Brain Tumor in the Newborn Infant. P. F. Schatski, S. G. Mortati, and W. G. McCain.—p. 909.

255, No. 20 (Nov. 15) 1956

Current Treatment of Infantile Hydrocephalus. D. D. Matson.—p. 933.
* Passive-Active Immunization in Certain Viral Diseases That Produce Permanent Immunity. J. Stokes Jr.—p. 943.
Cobalt-Induced Myxedema: Report of a Case. J. S. Robey, P. M. Veazey, and J. D. Crawford.—p. 955.

255, No. 21 (Nov. 22) 1956

Acute Hemorrhage from Peptic Ulcer: A Follow-up Study of 310 Patients. A. B. Chinn, A. S. Littell, G. F. Badger, and A. J. Beams.—p. 973.
Observations on the Glitter-Cell Phenomenon. L. B. Berman, G. E. Schreiner, and J. O. Feys.—p. 989.
* Studies in Cystic Fibrosis of the Pancreas: A Simple Test for the Detection of Excessive Chloride on the Skin. H. Shwachman and N. Gahm.—p. 999.

255, No. 22 (Nov. 29) 1956

Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Plasma of Normal Subjects After Ingestion of Erythromycin or Penicillin or Both. W. F. Jones and M. Finland.—p. 1019.
Studies in Regional Heparinization: I. The Use of Simultaneous Neutralization with Protamine—Preliminary Studies. L. A. Gordon, V. Richards, and H. A. Perkins.—p. 1025.
Nonbacterial Regional Lymphadenitis ("Cat-Scratch Fever"): Evaluation of Surgical Treatment. W. T. Small and R. C. Sniffen.—p. 1029.
Gastroenterology. S. M. Jordan, E. D. Kiefer, S. A. Wilkinson, F. E. McDonough, J. R. Ross, and J. M. McGrath.—p. 1042.
* Mumps and Presternal Edema. L. E. Braverman and I. Gershman.—p. 1048.
Editorial: Antibiotic Combinations.—p. 1057.

255, No. 23 (Dec. 6) 1956

Studies in Regional Heparinization. II. Artificial-Kidney Hemodialysis Without Systemic Heparinization—Preliminary Report of a Method Using Simultaneous Infusion of Heparin and Protamine. L. A. Gordon, E. R. Simon, J. M. Rukes, V. Richards, and H. A. Perkins.—p. 1063.
* Some Preoperative Warnings of Potential Operating-Room Deaths. J. E. Eckenhoff.—p. 1075.
Gastroenterology (Concluded). S. M. Jordan, E. D. Kiefer, S. A. Wilkinson, F. E. McDonough, J. R. Ross and J. M. McGrath.—p. 1084.
The Rocking Bed and Head Position. T. H. Joos, D. G. Dickenson, N. S. Talner, and J. L. Wilson.—p. 1089.
Incidence of Pathogenic Serologic Types of Escherichia Coli Among Neonatal Patients in the New England Area. M. Curtin and S. H. Clifford.—p. 1090.

255, No. 25 (Dec. 20) 1956

* The Natural History of Prediabetes. W. P. U. Jackson and N. Woolf.—p. 1183.

255, No. 26 (Dec. 27) 1956

* Accidental Injuries to Children. R. G. Rice, G. W. Starbuck, and R. B. Reed.—p. 1212.
Pernicious Anemia in Childhood. T. D. Stevenson, J. A. Little, and L. Langley.—p. 1219.
Congenital Esophageal Stenosis: Report of a Case of Annular Muscle Hypertrophy at the Esophagogastric Junction. L. L. Vargas, R. C. Britton, and E. N. Goodman.—p. 1224.
Rheumatic Heart Disease in the Framingham Study. J. Stokes III and T. R. Dawber.—p. 1228.
Physical Medicine and Rehabilitation. A. L. Watkins.—p. 1233.

256, No. 1 (Jan. 3) 1957

Serial Liver-Function and Blood Studies in Patients Receiving Chlorpromazine. R. Dickes, V. Schenker, and L. Deutsch.—p. 1.

256, No. 2 (Jan. 10) 1957

* Myxedema Induced by Prolonged Iodide Administration. H. M. Rubinstein and L. Oliner.—p. 47.
Anaphylactoid Reaction to Penicillin V and G Administered Orally: Report of 2 Cases and Brief Review of the Subject. H. C. Maganzini.—p. 52.
Osseous Lesions in Urticaria Pigmentosa. F. G. Zak, J. A. Covey, and J. J. Snodgrass.—p. 56.
Antihistamine Therapy for Gingival Hyperplasia Due to Dilantin. R. A. Gaillard.—p. 76.

256, No. 3 (Jan. 17) 1957

* Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Plasma of Normal Subjects After Oral Doses of Penicillin, Oleandomycin, and Combinations of These Antibiotics. W. F. Jones Jr. and M. Finland.—p. 115.
Toxic Dermatitis Associated with Prednisone Therapy. C. D. Bonner and F. Homburger.—p. 131.

256, No. 4 (Jan. 24) 1957

Primary Aldosteronism: Report of a Case and Discussion of the Pathogenesis. D. Fine, L. E. Meiselas, J. Colsky, and S. Arenhorn.—p. 147.
* Effect of Intramuscular Injections of Benzathine Penicillin G on Some Acute-Phase Reactants. R. C. Haas, A. Taranta, and H. F. Wood.—p. 152.

Human Fetomaternal Passage of Erythrocytes. W. P. Creger and M. R. Steele.—p. 158.
Human Hemoglobin Types: Their Epidemiological Implications. J. V. Neel.—p. 161.
Staphylococci in a Community Hospital: I. Nasopharyngeal-Carrier Rate of Hospital Personnel on Maternity Wards and Antibiotic Sensitivity of the Staphylococci Isolated. W. P. Loh and R. B. Street Jr.—p. 177.
Staphylococci in a Community Hospital: II. Nasal-Carrier Rates of Newborn Babies and Their Mothers. W. P. Loh and A. Abiog.—p. 179.

256, No. 5 (Jan. 31) 1957

Renal-Function Studies in Polycystic Disease of the Kidneys: With Observations on the Effects of Surgical Decompression. N. S. Bricker and J. F. Patton.—p. 212.
Cerebrospinal-Fluid Transaminase Concentrations in Clinical Cerebral Infarctions: Preliminary Report. J. B. Green, D. S. O'Doherty, H. A. Oldewurtel, and F. M. Forster.—p. 220.

256, No. 6 (Feb. 7) 1957

* Hepatolenticular Degeneration (Wilson's Disease) as a Form of Idiopathic Cirrhosis. T. C. Chalmers, F. L. Iber, and L. L. Uzman.—p. 235.
The History of Histoplasmosis, 1906 to 1956. J. Schwarz and G. L. Baum.—p. 253.
Intramuscular Injection of Trypsin: Its Value as a Thrombolytic and Anti-Inflammatory Agent. K. M. Moser.—p. 258.
Prednisone Versus Cortisone in Acute Rheumatic Fever: Review of the Literature and Report of a Case. J. L. Fischetti and W. R. R. Granger.—p. 263.

256, No. 7 (Feb. 14) 1957

Poliomyelitis in Pregnancy: A Report of 79 Cases in Connecticut. M. E. Rindge.—p. 281.
* Value of Rectal Biopsies in the Diagnosis and Treatment of Schistosoma Mansoni Infections. C. L. Spingarn, M. H. Edelman, T. Gold, H. Yarnis, and R. Turell.—p. 290.
Intramuscular Injection of Trypsin: Its Value as a Thrombolytic and Anti-Inflammatory Agent (Concluded). K. M. Moser.—p. 303.

256, No. 8 (Feb. 21) 1957

* The D-Xylose Absorption Test in Malabsorption Syndromes. J. A. Benson, P. J. Culver, S. Ragland, C. M. Jones, G. D. Drummey, and E. Bougas.—p. 335.
Benzathine Penicillin G: Its Effectiveness in the Prevention of Streptococcal Infections in a Heavily Exposed Population. J. Davis and W. C. Schmidt.—p. 339.

256, No. 9 (Feb. 28) 1957

* Traumatic Torsion of the Lung. D. C. Daughtry.—p. 385.
Changing Maternal Mortality in Massachusetts. J. F. Jewett.—p. 395.
The Natural History of the Eccrine Miliarias: A Study in Human Ecology. F. Sargent II and H. L. Slutsky.—p. 401.

256, No. 10 (March 7) 1957

Stenosis of the Sphincter of Oddi. R. B. Cattell, B. P. Colcock and J. L. Pollack.—p. 429.
Recurrent Miliary Tuberculosis. J. J. Leonard, S. Katz, and G. McCormick.—p. 435.
The Natural History of the Eccrine Miliarias: A Study in Human Ecology (Concluded). F. Sargent II and H. L. Slutsky.—p. 451.
* Acute Thyroid Poisoning: Report of a Case. R. P. Levy and W. G. Gilger.—p. 459.
Diversion of Urine to the Intestines as a Factor in Ammoniagenic Coma. W. V. McDermott Jr.—p. 460.

256, No. 11 (March 14) 1957

* Cysticercosis Cerebri: A Diagnostic and Therapeutic Problem of Increasing Importance. J. C. White, W. H. Sweet, and E. P. Richardson Jr.—p. 479.
Tracheitis Sicca: Successful Enzymatic Treatment with Pancreatic Desoxyribosenuclease (Dornase). B. Lynch, E. E. Clifton, and J. Lewis.—p. 495.
The Tetracyclines. L. E. Putnam.—p. 514.

256, No. 14 (April 4) 1957

Prevention of Infection in Surgical Wounds. R. Adams.—p. 625.
Stokes-Adams Disease: A Historical Review. F. G. MacMurray.—p. 643.
Chlorpromazine Dermatitis: Occupational and Immunochemical Aspects. N. E. Levan.—p. 651.
Periodicity in Disease. H. A. Reimann.—p. 652.

Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus Group B, Type 3.—The authors report the case of a newborn infant whose mother had an upper respiratory infection characterized by coryza, sneezing, and malaise. Two days after onset, placenta praevia was diagnosed and a cesarean section was performed. Several hours after birth the baby developed a croupy cough when crying and an inspiratory crow. On the third day fever developed; the patient became lethargic and ate poorly. The only findings on physical examination were physiological jaundice and

pedal cyanosis. A white cell count was 25,000, with 49% neutrophils. Throat and blood cultures were negative. The infant was given antibiotics and seemed better for one day, but was febrile again a day later. Chest x-ray was said to show bilateral atelectasis. Lumbar puncture showed 2+ Pandy test and 1.32 cells, 95% mononuclear, with a normal sugar level. The patient was transferred to Children's Medical Center, where she was found to be febrile, with respiration rate 35, moderate jaundice, a basal systolic murmur, and a palpable liver 2 cm. below right costal margin. Lumbar puncture, repeated, was the same as before. White cell count, 31,200, with 14% neutrophils, 18% band cells, 20% metamyelocytes, 2% monocytes, and 40% lymphocytes. Penicillin, streptomycin, sulfadiazine, and chloramphenicol were used. Nothing availed; the temperature remained between 100 and 101 F; the respiratory rate increased. The child died on the seventh day. Autopsy revealed cardiomegaly and hepatomegaly. There were no gross abnormalities in brain and spinal cord. Microscopically a diffuse myocarditis was found that involved chiefly the portions near the annulus fibrosis; the infiltration consisted of polymorphonuclear leukocytes, macrophages, and occasional lymphocytes. Also present were numerous eosinophils and degenerating leukocytes. In these areas degeneration of myocardial fibers and congestion of small blood vessels were found. No organisms or inclusion bodies were seen. The meninges of brain and spinal cord revealed edema and a diffuse infiltration with macrophages and occasional polymorphonuclear leukocytes. Two small foci of degeneration were seen in the cerebellum and also in the pons and considerable degeneration was seen in the spinal cord, especially the thoracic portion. A few small areas of infiltration were seen in the pancreas and adrenal cortex. From the spinal cord an agent was identified which was shown to be Coxsackie virus Group B, Type 3. The mother's serum three weeks after delivery showed strong neutralizing ability to this virus. In their discussion, the authors review the subject of myocarditis. The usual history is a sudden onset, with anorexia, evidence of circulatory and respiratory embarrassment and tachycardia, and rapid progression to recovery or death. Fever is slight. Pathologically, examination of the myocardium reveals either a granulomatous process or an inflammatory infiltrate, usually patchy, consisting of polymorphonuclear leukocytes, eosinophils, lymphocytes, and macrophages. The authors feel that certain evidence points to the fact that some of these cases may be manifestations of an infectious process not usually considered to produce such a condition. Many cases are seen in small children and infants over 6 months of age; perhaps because in the first 6 months the infant is protected by a maternal antibody. Some cases seem associated with an upper respiratory infection ending in interstitial pneumonia. This has occurred in a few small epidemics. The authors refer to Stoeber's review of the pathology of 140 cases of "epidemic myocarditis of infancy." The authors refer to several reports of nursery epidemics with a disease with myocarditis and occasional diarrhea and occasional meningoencephalitis. Stool studies in a couple of these cases produced Coxsackie virus Group B, Type 4. In one other, in a different nursery, Coxsackie virus Group B, Type 3 was found. In laboratory animals Coxsackie virus Group B, Type 3 has been shown to produce myocarditis in suckling and also adult mice. The authors state that pleurodynia and certain cases of aseptic meningitis are caused by Coxsackie virus Group B. Also, Group B viruses have been reported in association with a variety of clinical illnesses, including acute febrile illnesses either uncomplicated or resembling influenza, infectious mononucleosis, sinusitis, and appendicitis. The authors feel that there is enough evidence to suggest that this illness in their patient was caused by Coxsackie Group B virus, Type 3 and that since the child was removed from the mother at birth the transmission of the virus was presumably transplacental.

Passive-Active Immunization in Certain Viral Diseases That Produce Permanent Immunity.—The author puts forth the hypothesis that "deliberate exposure of man to certain living viruses by the natural route of infection during the period of immunity conferred by antibody passively transferred, either transplacentally from the mother or by parenteral injection, furnishes a satisfactory imitation of nature's adaptive method in these diseases without evidence of overt infection."

The problem of measles was compared briefly to that of other viral diseases such as epidemic viral hepatitis. In measles epidemics approximately 98% of the cases are both severe and overt, whereas in other diseases, as in epidmic viral hepatitis, the tendency of the natural disease is to be mild or even inapparent in a large percent of the cases. In the European and Philadelphia studies of measles, it appeared that overt disease seemed necessary for permanent immunity. Herrman, in New York, exposed a small group of infants in the

period of waning transplacental immunity to measles by using nasopharyngeal secretions from active cases. These infants were followed for several years through intimate exposures to measles, and the results suggested that immunity had occurred either with mild disease or without overt disease at the time of exposure in infancy.

The experience with viral hepatitis A occurred in three epidemics in three different institutions. In one study, one injection of 0.06 ml. of γ-globulin per pound of body weight was given to 248 inmates, whereas 264 were controls. In the injected group five cases with jaundice occurred (four in the first 5 days and one at 14 days) and four cases of hepatitis without jaundice occurred during same period. No other cases appeared. In the control group 44 cases in all occurred over next seven months. Since after six weeks there would not be enough γ-globulin to protect against hepatitis, and since there was continual exposure to hepatitis, it was suggested that a passive-active immunity had occurred. This was further tested by challenging 50 of the injected group and 4 volunteer controls with infective serum from the epidemic. Six of the fifty injected persons developed mild hepatitis and jaundice, and none had hepatitis without jaundice. In the four volunteer controls, one developed hepatitis with jaundice and three had hepatitis without jaundice. In the second institution student nurses were developing hepatitis. Of 36 nurses given γ-globulin (0.06 ml. per pound of body weight), one developed jaundice two days after injection and one had it eight months later. It was of interest that she did not work on the floors which seemed to be the source of the infection until six months after the injection. Of 20 other nurses who did not get γ-globulin, there were 6 cases of hepatitis with jaundice and 3 cases of hepatitis without jaundice. The same general findings of protection by γ-globulin (dose of 0.01 ml. per pound of body weight) and then failure to contract hepatitis, even though exposure occurred long after the effect of γ-globulin was gone, held true in a third institution.

Three theories were mentioned which attempt to explain the method of the phenomenon of passive-active immunity. First, the virus could possibly gain access more readily in the injected group and thus produce early inapparent infection. Secondly, the antibodies may remain fixed on lymphoid structures, macrophages, or Kupffer cells, even though all traces have left the circulation, and continue to fix the virus as it enters the host, either completely protecting or else permitting a mild or inapparent infection. Thirdly, some other disease in the controls, which the globulin had protected against in the injected, may have made them more susceptible to hepatitis. The author favors the second hypothesis.

A case concerning mumps is mentioned in which the infant of a mother who had CF antibodies to both soluble and virus antigen was sprayed with the active virus at 2½ and 3½ months of age. At 13 months his skin test was positive and he showed a good anamnestic response to the skin test.

This same principle is also being tested in poliomyelitis and appears to be holding true in this virus disease also.

The author feels that the passive-active immunization procedures may very well work out in infants. If necessary, one may assure the infant of antibodies to the virus one intends to feed it by active immunization of the mother.

Studies in Cystic Fibrosis of the Pancreas: A Simple Test for the Detection of Excessive Chloride on the Skin.—The authors report on a new, simple test for excess chloride on the skin. The finding of excessive Na and Cl in the sweat of patients with cystic fibrosis is well established. Most of the procedures are fairly time-consuming. The test consists essentially of making a finger or hand or foot impression on an agar surface. The test medium is made as follows: To make 500 ml. of the mixture, 25 mg. of agar is dissolved in 500 ml. of boiling water. When the agar is melted, add 4.2 gm. of silver nitrate and stir thoroughly. Then 2.5 gm. of potassium chromate is added to the mixture and stirred for a few minutes. The mixture is then poured into Petri dishes and stored in the refrigerator.

To perform the test, the print is made gently on the surface of the agar. If little chloride is present, the imprint is barely detectable. If much is present, an intense whitish-yellowish discoloration occurs immediately. If the hand is washed in water and dried just before printing, very little chloride will be present. Reactions rated as 1+, 2+, or 3+. Concentration of Cl of 60 mEq. per liter or less will give little or no reaction (+), whereas one of over 250 mEq. per liter will give an intense reaction (+++). If one dips a finger in a known concentration of NaCl, lets it dry in air, and then makes an imprint, a rough evaluation may be made of concentration. The procedure may be standardized by making

an imprint, then washing and drying the hand and having the subject remain in a warm room for 20 minutes, and then repeating the test.

The authors feel that this is a painless simple inexpensive test, taking little time and no skill to perform. Repeated tests on the same subject have given the same results. Since infants do not sweat much for the first 4 to 6 weeks, the test is of no value at that age, and the few newborns with meconium ileus tested gave a negative test. The authors mention the factors which may influence the chloride content of sweat. The concentration is higher in palmar than in body sweat, and in a few normals the palmar sweat was equal to the body sweat of patients with cystic fibrosis. Palmar sweat is more influenced by psychic stimulation. Higher environmental temperatures may increase the chloride content. It is also higher in winter than in summer. Rate and duration of sweating influences the content. The diet, the state of renal and adrenal function, and the presence of fever, dehydration, and, possibly, malnutrition are additional factors influencing the chloride concentration. The authors conclude with the statement that a 1+ reaction almost certainly rules out the possibility of cystic fibrosis.

Test Results

Reaction	140 Patients with Cystic Fibrosis	77 Healthy Infants & Children	140 Healthy Adults	103 Children with Miscellaneous Diseases	30 Siblings of Patients with Cystic Fibrosis	143 Parents of Patients with Cystic Fibrosis
+	0	65	128	82	20	78
++	2	12	11	17	13	43
+++	138	0	1	4	6	22

Mumps and Presternal Edema.—The authors report a case of mumps with presternal edema. This was in a 4½-year-old boy who had marked swelling of the submaxillary glands as well as the parotid five days before the appearance of the presternal edema. The presternal edema was subcutaneous, soft, slightly pitting, nonfluctuant, nontender, nonerythematous, noncrunching, ill-defined, and located over the manubrium and surrounding area. The course was benign, and the swelling subsided with the subsidence of the submaxillary and parotid swelling. This occurrence has been placed at from 1% to 6% in large epidemics in the armed forces. In most cases it is associated with severe submaxillary gland swelling. It is thought to be due to blockage of the lymphatic drainage of the upper sternal area due to the swelling of the submaxillary gland and surrounding tissues, impeding the flow of lymph at the level of the deep cervical nodes, which receive afferents from the superficial lymphatic vessels of the anterior thorax. This presternal swelling may also be seen in any condition leading to blockage of the subcutaneous lymph drainage of the anterior chest wall to the deeper subpleural and intermuscular vessels, as in sternal and retrosternal involvement in malignant lymphoma.

Some Preoperative Warnings of Potential Operating-Room Deaths.—The author emphasizes many of the causes of death in the operating room which are preventable. Under improper preparation of patients come the following items:

1. Food in the stomach. The author points out that no fixed interval between ingestion of food and anesthesia can be set, because emotion, apprehension, and injury can delay the emptying time of the stomach for many hours. The food should be removed by induced vomiting, because a Levin tube is not satisfactory. If vomiting cannot be induced and the operation is an emergency, then local or regional block anesthesia should be used if possible. If not, a cuffed endotracheal tube should be used. The vomiting of food is not always involuntary. Occasionally surgeons have manually deflated a stomach, inducing aspiration.

2. Apprehension. The author has seen four deaths which were unexplainable; however, the patients were extremely apprehensive and thought they were going to die. He points out the importance of preparing them with reassurance and with preoperative medication.

3. Hypovolemia. An anesthetized patients with reduction in blood volume has a decreased circulatory reserve; he may be unable to compensate for the depressant effects of anesthesia; he may be intolerant to sudden changes of position; he may demonstrate severe hypotension to relatively minor blood loss and is unable to compensate for major hemorrhage. This is especially seen in patients with neoplastic or ulcerative lesions of the large bowel, in those who have been bed-ridden or in body casts for long periods, in elderly persons who have

led a sedentary life, in those who have had extensive fluid loss for any reason, and in those who have had multiple operations. Some of the deficit should be made up before operation by transfusion.

4. Fever and dehydration. This is especially true of children; fever, dehydration, general anesthesia, and the accumulation of CO_2 form a combination that predisposes to convulsions. Except in the gravest emergency, hydration should be accomplished first.

5. Preoperative drug therapy. Several drugs are known to produce hazards during operation: (*a*) Cortisone. A patient who has been on cortisone previously may be in a state of relative adrenal exhaustion and during stress may not have circulatory compensatory control. Cortisone should be continued during operation. (*b*) Reserpine. Severe hypotension may develop in persons who have been on prolonged courses of reserpine up to within 10 days of operation, and the hypotension may persist for several days. (*c*) Chlorpromazine and promethazine. These predispose to hypotension in changes of position.

6. Failure to alert anesthetist to previous anesthetic difficulties—this is self-explanatory.

Hazards produced by preexisting disease unrelated to contemplated surgery:

1. Much of this is relative to adults with preexisting angina with or without myocardial infarction.

2. Cardiac arrhythmias. Patients with heart block are subject to cardiac arrest; unexplained tachycardia is often due to unsuspected heart disease or to low blood volume, and operation should be postponed until this has been worked out.

3. Patients with heart failure should be adequately prepared; one cannot digitalize the patient in the operating room.

4. Chronic respiratory disease. Emphysema is a particularly difficult situation because of poor gas exchange and inability to get rid of secretion; patients with asthma should not have thiopental, cyclopropane, morphine, or curare because of the possibility of bronchospasm; patients with chronic respiratory obstruction may compensate when awake or naturally asleep but not when anesthetized; a noncollapsible endotracheal tube should be inserted when the patient is awake, because it may be impossible to do it when he is anesthetized.

The author reiterates his feeling that alerting the anesthetist to pertinent facts in the patient's past medical history may be life-saving.

The Natural History of Prediabetes.—This article describes the case of a mother who had large babies and who eventually had a glucose-tolerance curve characteristic of diabetes, although she had no symptoms. Her next-to-last baby died in the neonatal period and demonstrated hyperplasia of the islet cells of Langerhans and also extramedullary hematopoiesis in the liver. At that time her glucose-tolerance curve was normal.

Accidental Injuries to Children.—This article is a report of a method of attack on accidental injuries to children in a community, namely, Greater New Bedford, Mass. One of its main functions was the collection of the community data and presenting them to a local committee consisting of leading citizens of the community; local and state legislators; clergy; representatives of the health, fire, police, and school departments; druggists; master barbers, and other groups. Instead of this group having discussed accidents as reported, it gradually evolved into a forum where the general problems of accident causation in the community have been discussed. It was requested that all accidents be reported by local doctors, the hospital, the schools, fire department, and police department. The physicians did not cooperate too well in the reporting. It was impossible to evaluate the project after a year because of several local variables, such as physicians not turning in reports; with more insurance coverage more cases are being referred by physicians to accident rooms, where better facilities exist for minor surgery. It is thought that a survey five years later, paying particular attention to the number of projects still going on that were initiated by the study, might be more valuable. The statistics on accidents in one year were as follows: 1861 accidents, 55% slight, 39% moderate, 5% severe, 7% fatalities, 5% hospitalized; causes were falls 39%, impact 29%, cutting or piercing 12%, bites 6% (mostly dogs), poisons (swallowed) 5%, burns 3%, crushing 3%, foreign body 2%. Under one year there was no sex difference; over one year boys had twice as many accidents (there was little difference regarding motor vehicle accidents, and there were more injuries indoors to older girls than to older boys).

Following are some of the measures the citizens initiated:

1. School. Superintendent received authority to summon an ambulance to take children to hospital.

2. Burns. Fire Chief said treatment of minor and major burns was the same as 20 years ago; he asked for a report on approved methods of treating burns (which he has received).

3. Safety officer. It was brought out the police department had none, and one was obtained for part-time work; also, a fellowship was secured to send an officer to Northwestern University Traffic Institute.

4. A poison control center was established, and druggists planned a campaign to educate parents.

5. Highly flammable toys were discovered in common use, and this was publicized.

6. Demonstrations and talks to children on handling animals were expanded.

7. School safety education programs and playground safety programs, including teaching first aid to supervisors, were started.

8. Bicycle safety program was developed.

9. Baby sitter education course (five-hour course) was organized.

10. An experimental project of having families report over a three-month period, in log fashion, all accidents occurring in their home, their causes, and their prevention, was started in the hope of testing the effectiveness of this device in reducing accidents.

11. Public health nurses and student nurses were given programs in accident prevention.

12. Attempts were made to make physicians more aware of the magnitude of the problem and their responsibilities in alerting parents to common hazards that can be anticipated and prevented.

13. Water safety was emphasized; concerted efforts were made to teach swimming.

The authors feel that such a program as described is very important, but they state that there is no clear blueprint for each community to follow.

Myxedema Induced by Prolonged Iodide Administration.—The authors refer to reports in the literature on the occurrence of myxedema in previously euthyroid adults and children after the prolonged administration of large amounts of iodide for bronchial asthma and other pulmonary conditions. One case reported apparently followed a bronchogram with iodized oil.

The authors report the case of a 33-year-old woman who had taken large doses of iodides for six years because of bronchial asthma. After two years of this she noticed a slight enlargement in her neck. After four years there was a gradual onset of puffiness of eyelids, skin, and neck, with dryness of the skin. Loss of hair of arms and legs occurred, and hair on her head became finer. Speech became slow. On physical examination the thyroid gland was enlarged; the skin was cool, dry and thick; the tongue was thick, and speech was slow and deliberate. Tests done showed low BMR (−21% and −17%); protein-bound iodine (PBI) was 11.0γ per liter and remained elevated six weeks later, probably because of the previous iodide ingestion (some of which was iodopyrine). Radioactive iodine uptake and PBI^{131} determinations showed a rapid accumulation of the iodine by the gland, but there was a rapid discharge, with no secretion of PBI^{131}, suggesting inability of the gland to transform iodine into the organically bound form. A week later (off exogenous iodine) repetition of these studies showed that the gland avidly retained most of the iodine, and the lack of response to potassium thiocyanate showed that it was in the organic form. There was also a high PBI^{131} secretion rate, very similar to that seen in the "rebound phase" after antithyroid medication and in thyrotoxicosis. Other authors found that these studies became normal in about six weeks after iodides were stopped. The patient clinically became euthyroid at about that time. The authors showed that normal subjects given iodides showed this same "rebound phenomenon." They also tested antipyrine for its possible effect as an antithyroid drug, but it showed no effect. The authors believe that the syndrome results from a prolonged block in thyroid hormone synthesis due to persistent elevation of the serum iodide level. In attempting to determine why this syndrome was not seen more often the authors interviewed a large number of patients in a large pulmonary-disease clinic who had had iodides prescribed for a long time. They discovered that practically all the patients confessed that they took the medication intermittently, and the authors speculate that the intermittency may have been the reason for the failure of hypothyroidism to develop.

Antibiotic Combinations: Antistreptococcal and Antistaphylococcal Activity of Plasma of Normal Subjects After Oral Doses of Penicillin, Oleandomycin, and Combinations of These Antibiotics.—The authors point out the considerable interest in the past few years in the use of multiple antibacterial agents. The hope has been to (1) obtain

a potentiating or synergistic action, (2) broaden the spectrum of antibacterial activity, and (3) avoid or delay the emergence or overgrowth of resistant organisms. However, only a limited number of combinations has succeeded in doing this. In a previous paper the antibacterial action of plasma after ingestion of erythromycin or penicillin, or combinations, was tested. Antagonism was not demonstrated, but differences in activity due to differences in absorption were demonstrated.

In the present paper the authors used potassium penicillin G (buffered), oleandomycin, oleandomycin salt of penicillin G (unbuffered; two-thirds oleandomycin and one-third penicillin G), and a buffered compound containing two parts of oleandomycin and three parts of potassium penicillin G. The antibiotics were given before breakfast, and plasma was collected before and at one, two, five, and eight hours after. Streptococcus 98 and Staphylococcus 209P were test organisms.

To summarize the results, no enhancement with the combinations was found. Penicillin alone produced the most activity against penicillin-sensitive strains. Oleandomycin alone was least active, the combinations being intermediate. Oleandomycin was found to be much less active than erythromycin, to which it is related, erythromycin being from 4 to 32 times more active. Furthermore, there is complete cross resistance between oleandomycin and erythromycin in vitro and from one-fourth to over two-thirds of freshly isolated erythromycin-resistant strains of staphylococci are also resistant to oleandomycin.

Effect of Intramuscular Injections of Benzathine Penicillin G on Some Acute-Phase Reactants.—The authors refer to studies in which it was observed that, after the intramuscular injection of benzathine penicillin G, elevation of the sedimentation rate and appearance of C-reactive protein were apt to occur. The authors studied the effect of benzathine penicillin G injections on 40 children convalescent from rheumatic fever. Only those with normal temperature, sedimentation rate, and C-reactive protein, who had been off all antirheumatic therapy for two months, were selected. These children received an intramuscular injection of 1,200,000 units of benzathine penicillin G. Eleven other children who met the same criteria were given an intramuscular injection of 1,200,000 units of procaine penicillin G. Thirty-three other children were studied by consecutive monthly injections (at least three months) of 1,200,000 units of benzathine penicillin G.

Of the 40 children who received the single intramuscular injection of benzathine penicillin G, 22 (55%) showed the appearance of C-reactive protein, which persisted from one to five days; 17 patients (42.5%) showed a rise in the sedimentation rate which persisted for several days after the C-reactive protein returned to normal; 5 patients (12.5%) had a temperature elevation over 100.5 F (rectal), usually lasting about three days.

Of the 33 patients injected serially, 16 (48.5%) had at least one temperature rise after one of the injections. Some had a rise after more than one injection, especially if they had had a rise after the first one. There was a tendency for febrile reactions to be less frequent with successive injections.

Of the 11 children given injections of procaine penicillin G, none had fever or elevation of the sedimentation rate and only two had very small amounts of C-reactive protein in their serum.

The authors feel that it is the benzathine penicillin that is responsible for the reactions. They feel that it is probably not allergic, but they mention the fact that, in rabbits, the injection of adjuvants (which benzathine penicillin resembles) causes the production of Cx-reactive protein, which is analogous to C-reactive protein in man.

The authors point out that it is important that physicians be aware of these reactions, because they can give rise to suspicion of activity of the rheumatic fever.

Hepatolenticular Degeneration (Wilson's Disease) as a Form of Idiopathic Cirrhosis. The authors refer to reports of patients who had only liver abnormalities in families in which other siblings had full-blown Wilson's disease. They feel that many of these cases have been diagnosed as other forms of cirrhosis. Because of the reported benefit of dimercaprol (BAL) it is important to try and find these cases before neurological symptoms develop.

Two families are presented. The authors studied the oldest girl of the first family and both siblings in the second. The first contained three affected siblings among seven. Symptoms started at 15, 12, and 17 years. All three died of liver failure with cirrhosis. There were no neurological symptoms. The brain of the oldest girl contained five times the normal copper content.

The second family consisted of two siblings, both of whom were affected. The disease started at 5 years in one and 11 in the other. One had neurological symptoms which cleared with dimercaprol therapy. Kayser-Fleischer rings were noted in both, as well as in the oldest girl in the first family. The least affected in the second family was proved to have cirrhosis on biopsy and also increased copper content of the liver.

The authors discuss the laboratory aids in diagnosis. The blood level of alpha amino acid is usually normal and was so in two of the three cases. The urinary levels were elevated in all three. It may be necessary to examine three consecutive 24-hour specimens during a period of high protein intake. The authors state that only the de Toni-Fanconi syndrome, besides Wilson's disease, has amino-aciduria as a primary defect. Excessive amounts of specific peptides (N-terminal dicarboxylic acid residues) are found. A third abnormality in metabolism of nitrogenous substances consists of 24-hour urinary excretion of uric acid increased when compared with creatinine excretion and lower than normal levels of blood uric acid. This last abnormality has been reported by two groups, and it is not certain as yet whether it is a constant finding. The authors suggest that the peptiduria (due to an abnormal protein metabolism specific for the disease) may block the reabsorption of amino and uric acids.

Copper metabolism is abnormal in the disease. Increased amounts of copper may be found in liver and brain. A new technique for detecting copper in needle biopsy specimens of the liver is described. Cupruria is usually, though not invariably, found. It is found late in the disease, but it is not known whether it is an early finding.

A marked reduction in serum ceruloplasmin (α_2-globulin with eight atoms of copper tightly bound) is usually present.

In reviewing the reports in the literature the authors feel that some of the cases considered as familial cirrhosis and starting even in infancy may have been Wilson's disease. They also feel that the underlying defect is one in protein metabolism, producing an abnormal protein with an increased affinity for copper. They suggest that several syndromes may thus appear: (1) asymptomatic aciduria; (2) cirrhosis, chronic hepatitis, or Banti's syndrome; (3) typical hepatolenticular degeneration, or (4) predominantly neurologic pseudosclerosis.

Value of Rectal Biopsies in the Diagnosis and Treatment of Schistosoma Mansoni Infections.—The authors report their studies on 106 cases of schistosomiasis (S. mansoni). They compared the findings of ova in the stools with those from rectal biopsy of the first or second rectal valves with a bladder punch. The entire specimen was examined by compressing it between two slides. Ova were found in 99 patients (93%) by biopsy and in 88 (83%) by stool examination. However, the stool examination method often required more than one stool and took much longer. The ova were also classified into viable mature, viable immature, degenerated or dead ova, and empty shells. In 18 cases the stools did not yield ova, whereas the rectal biopsy did. In seven cases ova were found in stools but not in the rectal biopsy specimen. In only six of this group was an abnormal appearance of the rectal mucosa noted. The authors also checked the changes in ova counts before and after stibophen (Fuadin) treatment. They found that there was a marked loss of viable schistosomes. They feel that this method is particularly rapid.

The D-Xylose Absorption Test in Malabsorption Syndromes.—The authors point out that the oral glucose-tolerance curve does not always show expected results in malabsorption syndromes, or even in normal persons; furthermore, the endogenous blood glucose level may be affected by excretion and metabolism, as well as absorption. The pentose D-zylose is not phosphorylated in vitro and is not absorbed against a concentration gradient. It does not seem to undergo selective absorption; it is apparently unaltered by the liver, and a constant proportion of the amount given (about 40%) is excreted in the urine. The amount excreted is proportional to momentary plasma concentration and independent of the rate of urinary flow. A portion of the oral or intravenous dose is destroyed by the body. A few authors had reported the use of this sugar in malabsorption states.

The method of performing the test is as follows: All food and fluid are withheld for eight hours; the patient voids; he then is given 25 gm. of D-xylose (Pfanstiehl or Fisher) dissolved in 250 ml. of tap water; this is immediately followed by another 250 ml. of tap water; children are given a dose of 0.5 gm. per pound of body weight (10% solution), with a maximum dose of 25 gm.; the patient is kept at rest during the test; all the urine voided in the next five hours is collected; oxalated venous blood samples are drawn at

one-half, one, one and one-half, two, three, and four hours. All the test patients had normal urinary function. Larger doses of D-xylose tend to cause diarrhea. With present dosage most had some increased peristalsis and a few had one to three watery stools. The total amount of xylose excreted in the five-hour period is measured, and the xylose content of the blood samples is measured. Practically, it was found that there were rather wide ranges of values for blood xylose, and so the authors settled on a measurement of the blood xylose at two hours. If it was high then and yet urinary excretion was low, one would expect a renal factor as the cause of the low excretion. The Table shows the results in normal persons, patients with untreated sprue, and those with treated sprue.

TABLE 1.—*Results of d-Xylose Absorption Tests in 24 Normal Subjects and 28 Patients with Nontropical Sprue.*

Group	2-Hr. Blood mg./100 ml.	5-Hr. Urine gm.
Normal subjects:		
Mean±S.D.	36±16	6.5±1.2
Number	23	25
Range	15—70	4.1—8.2
Patients with sprue, untreated:		
Mean±S.D.	12±5	1.3±0.7
Number	5	5
Range	4—16	0.8—2.6
Patients with sprue, in remission:		
Mean±S.D.	19±11	3.0±1.2
Number	21	27
Range	2—46	0.9—5.9

It may be seen that in normals, about 6 gm., or 25%, is excreted in the first five hours. Although this does not represent total absorption, it is sufficient for separating normals from abnormals. There was very little overlap, even in the ranges, in the two groups. In another group, with gastrojejunostomies, there was not good correlation between xylose excretion in urine, stool fat losses, and state of nutrition, although the test did, in general, tend to reflect deficient absorption after partial gastectomy or in affections of the small intestine. Thus, there appeared to be definite value in this test. Although the values expressed in the article were found for adults, the test can be performed in children. Dr. Martin G. Wolfish et al., of Toronto, Canada, reported the use of this test in children with the dosage schedule already mentioned. They did not report urine values, but they found that all their normal subjects, as well as patients with fibrocystic disease and dystrophy due to insufficient nutrition, had levels of 30 mg. or more at two hours, whereas patients with malabsorption syndromes had flat curves.

Traumatic Torsion of the Lung.—The author calls attention to the large percentage of deaths caused by automobile, industrial, and farm machinery accidents and that approximately 25% are due to nonpentrating thoracic injuries. He could find only one case report of torsion of the lung, which was diagnosed at autopsy in a 6-year-old child.

He reports a case of a 7-year-old girl who fell from her father's car, which apparently passed over the middle portion of her body. She suffered a fractured femur, laceration of the left forearm, and abrasions of the scapula, and also fractures of left 5th-9th ribs in the midaxillary line. Breath sounds were diminished over the left lower portion of the thorax, as was expansion. X-ray of the chest also revealed that the prominent vascular pattern of the left lung swept superiorly and slightly laterally rather than downward and laterally. A few hours later the left thorax showed a homogenous opacity of moderate density, but presenting a definitely granular appearance. An intercostal catheter produced no drainage. An exploratory laparotomy, because of a silent abdomen, revealed a ruptured spleen. She continued to have temperature elevation for a week and elevated pulse, respiration rate, and white cell count. These then gradually decreased, but remained elevated. Chest x-ray showed a rather diffuse homogenous opacity on the left, with a slightly ground-glass appearance. Six weeks after injury an exploratory thoracotomy was performed and revealed a torsion of the left lung, with only a small segment still viable.

The author points out that this condition can be corrected and that the early diagnosis may be life-saving. The characteristic x-ray picture is that of a vascular pattern which radiates superiorly and laterally. If, however, the x-ray is delayed, only a homogenous density may be seen. As to etiology, he believes that it is due to compression of the lower thorax,

which deflates and displaces the lower lobe medially and upward, tearing the thin inferior pulmonary ligament. The sudden release of the thoracic compression caused the aerated upper lobe to fill the high-vacuum space in the lower thorax by rotating clockwise.

Acute Thyroid Poisoning: Report of a Case.—The author reports the case of a 15-month-old child whose sister fed him 50 one-grain (65 mg.) tablets of thyroid U. S. P. six hours before admission.

On physical examination he was acutely and gravely ill, markedly irritable, tense, and hyperirritable. Midriasis was present (pupils reacted to light). The skin was warm and dry. The temperature was 104 F; pulse rate, 200, and blood pressure, 120/68.

The patient was managed as a case of thyroid storm (but without the antithyroid drugs)—put in a cool croupette, given O_2, barbiturates, vitamins, and forced fluids and food (treatment designed to reduce activity, supply increased demand for O_2, reduce fever, and satisfy excessive demand for fluid and calories). Improvement was rapid.

Of interest were the studies of protein-bound iodine (PBI), cholesterol, and radioactive I^{131} uptake. Cholesterol fell to a low level 6 days after ingestion and returned to normal about 11 days later. The PBI was 19.5γ /100 ml. and fell in a straight line to 5.0γ on the 11th day, which was probably normal. Radioactive I^{131} uptake was only 4% seven days after ingestion, probably showing an inhibitory effect on the pituitary of the increased circulating thyroid hormone. Sixteen days later it was 18.3%, in a normal range.

The authors point out the rarity of poisoning from dessicated thyroid. In this case the symptoms, although alarming, subsided rapidly but abnormal thyroid function was present for about 11 days. Five months later the youngster's thyroid function had remained normal.

Cysticercosis Cerebri: A Diagnostic and Therapeutic Problem of Increasing Importance.—In a period of two years the diagnosis of cysticercosis, or infection of the human brain with the larval form of the pork tapeworm, has been made three times at the Massachusetts General Hospital. The authors feel that conditions in certain places in this country are favorable for the development of this disease and also that the return of troops from overseas areas where it is prevalent will also make this disease commoner.

The natural history is as follows. Man is the definitive host. He ingests the encysted larva in insufficiently cooked pork. The larva develops into the adult in the human intestinal tract. Its egg-bearing segments are discharged in the feces. When the eggs are eaten by the pig, they hatch into larval forms and burrow into the blood stream, eventually encysting in muscle. If man ingests the eggs from contaminated food they hatch in his intestinal tract, burrow into the blood stream and encyst in various tissues, the brain being the commonest site in man.

Three varieties of infection in the human brain have been described: (1) Cysts, usually single, give rise to symptoms suggesting a cerebral neoplasm; (2) widespread infection without localizing signs (more than 200 cysts have been counted in a single brain)—usually accompanied by increased intracranial pressure, papilledema, visual impairment, and mental changes—commoner in children—wide decompression may be palliative, but the prognosis is poor; (3) hydrocephalus from proliferative inflammatory reaction in the basilar meninges. Not infrequently there is a mixture of these types. Epileptic seizures are not uncommon. The spinal fluid may have a slight elevation of protein.

The diagnosis is usually difficult. Blood eosinophilia, spinal fluid eosinophilia, lymphocytosis, and increased protein level may be helpful signs. Intestinal infection is often absent. The complement-fixation test may be helpful, but it is often falsely negative. If positive, it may not be conclusive, because specificity of antigen is not absolute. X-ray evidence of calcification in the cysts may be helpful, especially if associated with calcification in muscle and subcutaneous tissue. Some authors feel that in the pneumoencephalogram the cysts may be differentiated from posterior fossa tumors because they do not cause deviation of the aqueduct of Sylvius or complete obliteration of the fourth ventricle the way posterior fossa tumors do. The treatment is surgical.

Pediatrics, Springfield, Ill.

19, No. 1 (Jan.) 1957

Editorial: Reviewing of Manuscripts. C. D. May.—p. 1.
The Treatment of Acute Lead Encephalopathy in Children. J. J. Chisolm Jr. and H. E. Harrison.—p. 2.
Congenital Defects of the Lymphatics in Infancy. J. B. J. McKendry, W. K. Lindsay, and M. C. Gerstein.—p. 21.

Acute Staphylococcal Pericarditis. J. M. Horan.—p. 36.
Pheochromocytoma in Children: Report of 3 Familial Cases in 2 Unrelated Families. T. E. Cone Jr., M. S. Allen, and H. A. Pearson.—p. 44.
Spectrographic Comparison of Ranges of Vibration Frequency Among Some Innocent Cardiac Murmurs in Childhood and Some Murmurs of Valvular Insufficiency. T. N. Harris, H. A. Saltzman, H. L. Needleman, and L. Lisker.—p. 57.
Further Observations on Homeostatic Disturbance in Acrodynia. D. B. Cheek.—p. 68.
Hemophilus Influenzae Type b Cellulitis. M. Green and M. D. Fousek.—p. 80.
Neonatal and Maternal Thrombocytopenic Purpura Due to Quinine. A. M. Mauer, W. DeVaux, and M. E. Lahey.—p. 84.
The Treatment of Familial Hypercholesterolemia with a Plant Sterol. A. H. Levkoff and K. T. Knoble.—p. 88.
Persistent Diarrhea as the Predominant Symptom of Hirschsprung's Disease (Congenital Dilatation of Colon). E. M. Stockdale and C. A. Miller.—p. 91.
* Serious Untoward Reactions to Therapy with Cortisone and Adrenocorticotropin in Pediatric Practice (Part I). R. A. Good, R. L. Vernier, and R. T. Smith.—p. 95.
Psychiatric Study of Mentally Retarded Children of Preschool Age. K. F. Woodward and M. G. Siegel.—p. 119.
Apparatus for Collection of Urine from Female Infants. A. H. Heeley and N. B. Talbot.—p. 127.
Acute Respiratory Diseases: Etiologic, Diagnostic and Therapeutic Considerations. J. M. Adams.—p. 129.
Solid Intrathoracic Masses in Children. G. L. Boyd.—p. 142.
The Medical Aspects of Water Fluoridation. E. R. Schlesinger.—p. 156.
Clinical Conference: Tumor of the Heart. D. E. Cassels.—p. 162.

Serious Untoward Reactions to Therapy with Cortisone and Adrenocorticotropin in Pediatric Practice (Part I).—The serious complications of therapy with cortisone and corticotropin are discussed, first, by way of a presentation of complications that have been observed in the authors' experience and, second, by way of a review of the pertinent literature. Patient material is comprised of 340 children treated systemically with corticotropin and cortisone over a period of three years for a variety of conditions. Neglecting minor side-reactions, 33 patients were found to manifest undesirable consequences of therapy; all were considered to be of such a severity as to endanger the life of the child. These complications may be divided into several categories as follows: (1) disturbance of function of the central nervous system, (2) major intercurrent infection, (3) gastrointestinal disturbances, (4) electrolyte imbalance, (5) metabolic derangement, and (6) osteoporosis and pathologic fractures. Most frequently noted were severe infections, many of which were staphylococcal, resistant to the usual antibiotic therapy; it was also considered noteworthy that two cases of herpes zoster were found. Next commonest were complications involving the central nervous system, ranging from severe psychoses to thrombosis of the central retinal artery, and included were convulsions both with and without hypertensive encephalopathy. Disturbances of the gastrointestinal tract involved both perforation and bleeding. There were two instances of pathologic fracture with osteoporosis; six instances of severe electrolyte balance were observed; two instances of sudden or rapid death and one case of severe insulin-resistant diabetes mellitus were noted.

A review of the literature with a discussion of the disturbed physiology in these disorders is included. Further discussion of this problem is to appear in future publications.

Radiology, Syracuse, N. Y.

68, January, 1957

* Radiation Therapy of Neuroblastoma. William B. Seaman and Mark D. Eagleton.—p. 1.
* Nocardiosis: A Case Report and Brief Review of the Literature. Gunnar A. Gunderson and Charles M. Nice Jr.—p. 31.

68, February, 1957

* Hyaline Membrane Disease: Preclinical Roentgen Diagnosis; A Planned Study. S. B. Feinberg and M. E. Goldberg.—p. 185.

Radiation Therapy of Neuroblastoma.—Findings in 19 cases of neuroblastoma in children, which included microscopic analysis, formed the basis of this article. Five survived three years or longer following x-ray therapy. The authors believe that the remarkable improvement in recent years is due chiefly to the intelligent use of x-ray therapy, despite the bizarre performance, which seems to be the natural history of this neoplasm. Spontaneous regression and maturation into a more differentiated benign form takes place. Histologically verified metastases were present in two of the five surviving cases; one had liver metastases.

The literature records comparable results in other groups following roentgen therapy. Anderson reported recovery in a 7-month-old infant with an abdominal neuroblastoma with

femoral metastases, without any treatment except corticotropin. Stewart's case, which received x-ray to a proved metastatic neuroblastoma of the femur, remained well for 14 years following x-ray therapy.

One of the authors' cases which had extensive changes on roentgenograms is reported and illustrated in detail. There was a superior mediastinal mass, sutural diastasis, destructive osteoblastic reaction in the frontal bone, and diaphyseal periosteal reaction of the femora and humeri. These changes disappeared following x-ray therapy.

The method of treatment used in the 19 cases varied from 1300 to 3000 r delivered in 22 to 55 days, careful consideration being given to the clinical status of the patient. Radiation damage to adjacent normal tissues may be unavoidable if a clinical cure is the goal.

Phillips suggests that spontaneous regression or differentiation into ganglioneuroma may be enhanced by a variety of agents such as x-ray, nitrogen mustard, cortisone, anti-folic-acid drugs, and surgical trauma. Uhlmann believes that radiation therapy may not destroy all of the tumor cells but may initiate cellular changes leading to maturation and control of the disease. Hicks demonstrated that in animals the neuroblast is the only radiosensitive cell in the developing nervous system.

Because of the occasional survival of patients who have metastases, extensive spread of the disease should not be a contraindication to x-ray therapy. A high survival rate seems to occur in the younger age groups.

Nocardiosis: A Case Report and Brief Review of the Literature.—Nocardiosis, named after Nocard, who in 1888 first described this disease in cattle on the island of Guadeloupe, in the French West Indies, was in 1943 (Waksman and Lechevalier) recognized as more or less of an entity because of a new classification for the order Actinomycetales. Because of marked cultural differences, the genus Nocardia was separated from the accepted genus Actinomyces. Nocardia is sometimes acid-fast and aerobic, differing from Actinomyces. Nocardiosis in man may be caused by any one of nine species, but N. asteroides is the usual agent in North America.

A newborn, apparently normal, infant, weighing 8 lb. at birth, developed "coughing spells," and a roentgenogram showed several pulmonary infiltrates. A papular, pustular rash appeared on the scalp, thorax, abdomen, face, and groin. After nine days Gram-positive bacilli were found in a blood culture. At 3 months, osteomyelitis of the toe became evident, but the lung disease had partially regressed. Two bouts of pneumonia followed later. Actinomyces was searched for in vain. At the age of 2 years, shotty lymph nodes were found. The pulmonary infiltrates fluctuated but remained present on chest roentgenograms. Late in the sixth year, a fluctuating mass over the thyroid revealed N. asteroides. The fungus was positively identified after death in the lungs, liver, kidneys, and spleen. Hepatic calcifications were present.

The species found in this instance causes an acute lung infection, which becomes chronic and has a tendency to spread to other organs. The infection is manifested by malaise, weight loss, afternoon fever, and mucoid sputum. Infection commonly metastasizes to the brain and soft tissues. Abscesses of superficial tissues frequently develop, and multiple draining sinuses are prone to develop. Chest roentgenograms show either small or large infiltrates or consolidations. There is great variation of bone destruction, proliferation of fibrous tissue, and formation of cavities. Remissions occur, and the patient may be asymptomatic for as long as 11 months. Despite active disease, fever may not be present. The leukocyte count may reach 50,000.

The sulfonamides appear to halt and perhaps heal nocardiosis. It should be considered when a relatively healthy-appearing child has extensive lung infection demonstrable radiographically, with pustules appearing on the skin shortly thereafter. The finding of Gram-positive cocci, blood, and pus should be another clue. Lack of response to the newer antimicrobials may also be suggestive of a fungous infection.

Hyaline Membrane Disease: Preclinical Roentgen Diagnosis; A Planned Study.—Newborn infants with hyaline membrane lining alveolar ducts and producing a varying degree of alveolar collapse are usually premature, delivered by section, or born of a diabetic mother. The diagnosis depends largely upon recognition on roentgenograms of granular shadows and increased bronchovascular patterns distributed more or less evenly in both lungs. The relative aeration is due to air-filled alveolar ducts.

The authors attempted to evaluate early roentgen changes prior to the manifestation of respiratory distress. The first film was taken as early after birth as possible, always within the first hour of life. Follow-up films were made at 2-, 4-, 8-, and 24-hour intervals. Of 89 infants followed, 8 had histologically proved hyaline membrane disease. Two had apparent

disease and survived. In seven of the eight cases unequivocal abnormality was demonstrated on the initial film. The 1- and 2-hour films were of the greatest diagnostic value. Clinical signs in two cases made their appearance after six and nine hours, respectively. At this time the respiratory rate began to increase, reaching 60 per minute in the next 24 hours. Clearing started at 48 hours. In seven cases symptoms developed within 15 minutes to 3 hours after birth, at which time labored respirations, sternal and costal retraction, and cyanosis were noted.

The subtle but definite early granularity which advanced to diffuse lung changes after the onset of symptoms was not encountered in the normal, or non-hyaline-membrane-problem, cases.

Early alertness to the finely granular and increased bronchovascular patterns, before the development of physical signs, might lead to anticipation of the diagnosis earlier than it has heretofore been expected.

Rivista di clinica pediatrica, Florence

57, January, 1956

* Cortisone and ACTH in the Cure of Tuberculosis in Children. C. Cocchi.—p. 1.
The Alkali Reserve: Diffusible Calcium Ratio; Its Value with Regard to Ionic Calcemia. G. Mangione, S. Le Brun, N. Loddi, and A. Pandolfini.—p. 21.
* Clinical, Hematological, and Serological Observations of Patients During an Epidemic of Rubella. G. Biscioni and E. Tosi.—p. 28.
Secondary and Sub-Clinical Forms of Acquired Immunologic Hemolytic Anemia. G. Gelli.—p. 40.
Two Cases of Osteogenesis Imperfecta. G. Aceto and A. Ziccolella.—p. 55.
Hypo-Alimentation in the First Week of Life: The Behavior of the Proteins and Lipo-Proteins. P. Moggi.—p. 64.
Paper Chromatography of Proteins (Hemoglobins). G. Rapi and M. Dettori.—p. 80.

Cortisone and ACTH in the Cure of Tuberculosis in Children.—Cortisone, or a related drug (hydrocortisone, corticotropin [ACTH], prednisone), is being used routinely in the treatment of tuberculosis in children at the Pediatric Clinic in Florence. Excellent results have been obtained, not only in cases of tuberculous meningitis but also in cases of pleurisy with effusion, miliary tuberculosis, and erythema nodosum.

Cortisone acts to disturb the normal defenses of the body. It overcomes the allergic manifestations to the tubercle bacillus and also seems to prevent the walling off of the bacilli. In tuberculous meningitis, it will usually prevent blockage of the spinal fluid and also lower its protein content. This action will better expose the bacilli to the destructive action of the antibiotics.

Large doses of cortisone are dangerous and must not be given. Cortisone therapy must always be accompanied by antibiotics. Recommended doses are cortisone 0.5 to 1.0 mg. per kilogram per day, streptomycin 10 mg. per kilogram per day, and isoniazid 10 mg. per kilogram per day. Viomycin may be given if the tubercle bacilli are resistant.

At the present time, the percentage of recoveries in cases of tuberculous meningitis at the author's clinic is over 97%. The recovery is much more rapid than was the case before cortisone was given. The regimen in use at present is as follows: intramuscular injections, streptomycin 300 to 500 mg. per day and isoniazid 500 to 900 mg. per day; lumbar injections, streptomycin sulfate 20 to 30 mg. and isoniazid 20 to 40 mg.; cisternal injections, isoniazid 20 mg. Hydrocortisone 2.5 mg. is given alternately with the lumbar and cisternal injections.

Clinical, Hematological, and Serological Observations of Patients During an Epidemic of Rubella.—Data are presented from 29 patients seen during an epidemic of rubella in Pisa in the spring of 1955. The outstanding finding was enlarged lymph nodes; an exanthem was not always present; only one patient had a fever, and none had an enlarged spleen. Hematologically, the striking feature was the large number of monocytes and plasmacytes.

News and Comment

ANNOUNCEMENTS

Health Education Conference.—The 1958 Eastern States Health Education Conference of The New York Academy of Medicine will be held on Thursday and Friday, April 24 and 25, 1958, at the Academy, 2 E. 103 St., New York.

Easter Seal Research Foundation Grants.—The Easter Seal Research Foundation of the National Society for Crippled Children and Adults provides grants-in-aid for investigations concerned with the prevention and treatment of physical and associated disabilities and with the rehabilitation of the physically handicapped. Disabilities may be congenital or may result from accident or illness. Accident prevention, per se, is outside the scope of the Foundation's research interest.

Funds for research grants are derived from a fixed percentage of the gross returns of the annual Easter Seal campaign conducted by the National Society and its state and local affiliates.

The Foundation is concerned with investigations of (1) the causes of crippling, (2) the prevention of physical disabilities, (3) methods for improving impaired functions or for mitigating the results of dysfunction, and (4) measures for enhancing the effectiveness of the rehabilitation process. Research projects may involve basic or clinical research or both.

The Foundation invites applications for grants-in-aid. Applications filed between Sept. 1 and March 31 are reviewed in June. Applications filed between April 1 and Aug. 31 are reviewed in November. Awards are announced during the months of June and November.

Residency in Pediatric Oncology.—Applications for the residency from July 1, 1958, to June 30, 1959, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases, in New York, will be received up to Nov. 1, 1957. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary is $3600 annually plus maintainance. For application forms and information write to Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Residences in Pediatric Pathology.—Residency positions are currently available in pediatric pathology and in hematology at the Children's Hospital of Michigan. The pathology department is included in The Department of Laboratories, under the direction of Wolf W. Zuelzer, M.D., and is associated with an active hematology clinic and research laboratories. Clinical conferences and ward rounds are held regularly, and during the school year the hospital is the Pediatric Teaching Service of Wayne State University School of Medicine.

Positions are now available for one year, starting at any time. Training is recognized by the American Boards of Pediatrics, Pathology, and Radiology and the Canadian Board of Pediatrics. The annual stipend is $2400 and room and board.

Please address all inquiries to Jay Bernstein, M.D., Department of Pathology, Children's Hospital of Michigan, 5224 St. Antoine St., Detroit 2.

Books

BOOK REVIEWS

A Guide for the Study of Exceptional Children. By Willard Abraham. Price, $3.50. Pp. 276. Porter Sargent, 11 Beacon St., Boston 8, 1956.

This paper-bound edition is well indexed and, as the name implies, is a "guide" to further study of eight specific areas in the field of the exceptional child, namely, the bilingual, emotionally maladjusted, gifted, and hearing, visual, orthopedic, speech and mentally retarded child. There are forty-two pages repeated for the "general guide" outline, but the "specific guide" is different in each category.

Possibly the greatest strength in this book is the sixty-eight-page bibliography, with many annotations, which is divided into the eight subject areas. This is followed by the discussion of the individual topic. At the end of the book is a list of ninety helpful periodicals, a general and specific film list, and a medical glossary.

Of particular interest is Dr. Abraham's inclusion of short excerpts from previously published works, such as W. Somerset Maugham's "Of Human Bondage," Stephen Corey's "The Poor Scholar's Soliloquy," and G. H. Reavis' "The Animal School." The short description of the Verde Valley School for Gifted Children at Sedona, Ariz., is unique with its high teacher-low student ratio and its specialized accelerated program.

The brief outline of the 1954 Arizona State College Summer Workshop at Tempe shows the center of the participant's interest to be on the child who is gifted (thirty), bilingual (thirteen), or mentally retarded (eleven) or who has reading disabilities (ten), speech and visual disabilities (eight), orthopedic disability, or emotional maladjustment (seven each), with total of eighty-six participating.

The guide is particularly suited to use by educators, students, and parents but should not be overlooked by medical personnel, since it has much to offer to the pediatrician, public health nurse, and medical social worker. Dr. Abraham points out that four million children need help but that only one in every ten is receiving assistance and that one child in every eight is a deviate, bringing the problem pretty close to home.

Retarded Children Can be Helped. By Cornell Capa and Maya Pines. Price, $5.00. Pp. 159, with about 80 illustrations. Channel Press, Great Neck, N. Y., 1957.

This small, and unduly expensive, book is full of text and pictures which appeared in *Life* magazine three years ago, which have been nicely expanded. In its ten chapters the authors discuss the national magnitude of the problem of mentally retarded children and their parents, and in some detail explains present facilities at all stages of development. These include discussion of nursery schools, the visiting nurse's role in home planning, educational and workshop facilities, the role of community efforts, and detailed orientation as regards institutions and training schools for the mentally retarded.

The text of the book is well written but suffers from the tendency to oversimplify matters of extreme complexity as regards the diagnosis and eventual disposition of mentally retarded children. The implication of the text frequently seems to be that if enough pressure is brought to bear on the medical profession and legislators of state and federal governments—excellent facilities will automatically result. This concept is only partially valid as judged by the many misguided and misdirected efforts which can result from unintelligent and over-emotional planning. On the other hand, this book does serve an extremely useful purpose in appraising parents of the fact that they are not alone in their problems, that facilities do exist in almost every area of the country for diagnostic services, and that parents' groups form a valuable means of exchange of information and the channeling of the natural desires to help each mentally retarded child and his family. The real apathy of many members of the medical profession, the medical schools, and many state health departments is painfully stressed, and probably with much justification. There has been a need for such a book to supplement the counseling which pediatricians are frequently called upon to give.

Pediatric Dentistry. By M. Michael Cohen. Price, $14.75. Pp. 607, with 395 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

The author, with the assistance of many eminent associates, presents an extremely complete book concerning dentistry for children. As the title indicates, the general theme is to consider the child as a whole, rather than specific considerations about the teeth and mouth, alone.

Subjects presented cover a wide range of topics, with almost equal emphasis being placed on didactic subjects as well as clinical techniques. Probably the major criticism from a dentist's viewpoint is the lack of completeness in the dental techniques such as operative dentistry, diagnosis, pulp therapy, and space maintenance. Coverage in the fields of oral surgery, handicapped children, and oral manifestations of systemic diseases is unusually thorough.

The descriptions and print are explicit and lucid. The diagrams by Ullrich are excellent. Though many are not original, the photographs throughout are plentiful, large, and clearly reproduced. The text completes its purpose as a good reference for students and practitioners of not only dentistry but also medicine.

Services for Children with Vision and Eye Problems. Prepared by Committee on Child Health, American Public Health Association. Price, $1.50. Pp. 112. American Public Health Association, 1790 Broadway, New York 19, 1956.

This pamphlet contains much important information for all those concerned with vision testing and conservation. Its scope is sufficiently broad to justify changing the subtitle to "A Guide for Professional Personnel." It emphasizes the concept of dividing preventive measures into "primary" (those used to prevent injury or loss of vision) and "secondary" (those used to prevent existing visual handicaps from injuring the child's personality). It was a pleasure to find the statement that "Ideally all children should have the benefit of a complete eye examination during the preschool period." It also wisely cautions against the practice of overinstitutionalization of children with visual defects.

Perhaps the virtues of simple Snellen test might be reinforced a little more, and definitions of such terms as oculist, optometrist, and optician might be included.

Services for Children with Hearing Impairment. Prepared by Committee on Child Health, American Public Health Association. Price, $1.50. Pp. 124. American Public Health Association, 1790 Broadway, New York 19, 1956.

This pamphlet contains much valuable material which is not readily available elsewhere. It is stated clearly, concisely, and briefly, and the concept of the program suggested is sufficiently flexible to apply to the varying circumstances of individual communities. It gives sound advice regarding the selection, use, and care of hearing aids. It also gives a brief but detailed explanation of several treatment procedures, such as the section "Auditory Training." It offers an up-to-date discussion of special services and facilities which may be involved. It also emphasizes the point that hearing impairment often means loss of understanding rather than total loss of hearing.

Perhaps the subtitle should be broadened to "A Guide for Professional Personnel." The inclusion of a sample record form might be desirable, and on page 35 the steps of the screening procedure might be given in a more logical sequence, such as: (1) initial screening, (2) rescreening, (3) audiometric testing, (4) obtaining a history from the parents, (5) referral to an otologist.

The Compleat Pediatrician. By W. C. Davison and Jeana Davison Levinthal. Seventh edition. Price, $4.25. Pp. 265. Duke University Press, College Station, Durham, N. C., 1957.

The seventh edition of this popular reference book on pediatrics has just been published, bringing up to date the innumerable points of diagnosis and therapy encountered in pediatric practice. This book has been based on the principle that a busy physician needs a quick complete source of reference to help him recall any condition that might account for any set of presenting symptoms and to provide him with up-to-date advice on therapy. In addition, complete tables are available giving the facts of normal growth, development, and laboratory analysis.

Since discussion of controversial subjects is at a minimum, readers may object to the dogmatic way in which some of the subjects are presented. If one recognizes, however, that this is primarily a compendium of facts and that a given plan of therapy represents only the opinion of one group, this need not be an important objection.

There is a wealth of valuable information here that cannot be found elsewhere. This book can be recommended highly to all physicians to children.

Diseases of the Heart. By Charles K. Friedberg. Price, not given. Pp. 1161, with 55 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1956.

This second edition of Friedberg's book employs the same general approach as the first edition, with discussions of pathologic physiology and mechanisms of cardiac disorders receiving special emphasis in a very large and comprehensive work which includes almost all aspects of heart disease. Revisions in the new edition dictated by rapid advances in this field include additions to the discussion of newer graphic techniques in examination, revisions of the discussion of surgical techniques as applied to heart disease, discussion of newer concepts of medical therapy, and many other additions.

This volume is not particularly oriented toward pediatric cardiology, and much of its content will be of little or no value to the average pediatrician, although the discussions of rheumatic fever and congenital heart disease are very valuable. The discussions of diagnostic techniques, including electrocardiography, vectorcardiography, and radiologic examinations, will also prove of great value. The place of this book in pediatric circles would seem, then, to be one of a very authoratative reference source for the person interested in cardiac problems and particularly in the physiologic disturbances associated with these problems.

Sick Children. By Donald Paterson and Reginald Lightwood, Seventh edition. Price, $8.75. Pp. 593, with 82 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

In the new edition of this English textbook, the authors have tried to keep it both practical and helpful for the general practitioner and senior student. Diagnosis and treatment are emphasized, and the 593-page text is concise almost to the point of an outline. The book is a good introduction to pediatrics, but it is not comparable to those of Nelson, Holt, and McIntosh or to Dr. Paterson's new Canadian "Pediatrics," which he and Dr. McCreary edited.

After reading the book, this reviewer was again impressed with the phraseology of much English medical writing, colorful and often delightful. Consider this description of the hand in Erb's palsy: "The arm hangs by the side, fully pronated, with the hand in the position of a waiter's hand bent to receive a surreptitious tip." Or, again, this picture of a child with rickets: "The rickety child has the head of a philosopher, the chest of a greyhound, the legs of a grand piano and the tummy of a poisoned pup." What nicety of expression!

The sections on respiratory infections, rheumatic fever, "the nervous child," disorders of the central nervous system, primary tuberculosis, and diseases of children in the tropics are exceptionally well done. The tropical disease section, especially, makes fascinating and instructive reading.

There are several appendices, and those which concern drug dosages and vitamin preparations should be most helpful, although many of the vitamin preparations are of English make. The appendix which deals with "electrolytes of the body fluids" in less than three pages is too superficial to be of value. The one which tabulates times of appearance of ossification centers is concise and clear; it should be helpful in determining osseous age in children over one year old, but it will not be of much value in infants.

The book is not documented with many references, which is probably understandable in a work which is intended to be practical and brief. There is not much material on growth and development except as it is incorporated into the general text. Several statements, some of which are here culled at random, might be questioned by many American pediatricians: the suggestion that the infant be held over the chamber after feeding, almost since birth, so that he is usually bowel trained by two to three months of age; the statement that laboratory investigations are not of great help in the early diagnosis of cretinism (protein-bound iodine levels are not mentioned); failure to mention the importance of sodium and potassium serum levels in the diagnosis of the adrenogenital syndrome; the apparent survival of a belief that irradiation of the thymus may be helpful and that status thymicolymphaticus is a disease entity; the recommendation that inguinal hernias not be repaired until eighteen months or two years of age; the suggestion that painting inflamed throats and tonsils with a weak solution of iodine may be beneficial.

Although this reviewer disagrees with some of the author's statements, the book is one of the better "short" texts on pediatrics. It is neither sufficiently complete nor comprehensive

enough to serve the needs of a pediatrician, but it does cover an amazing amount of pediatric pathology. It should fulfill its objective—to be practical and helpful to the general practitioner and senior student.

Pediatrics. Edited by Donald Paterson and John Ferguson McCreary. Price, $14.00. Pp. 654, with numerous illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

This volume is a general textbook of pediatrics designed primarily as a reference book for the practicing physician. The editors and collaborators represent the outstanding pediatricians of Canada. Almost all phases of pediatrics are included, but, by design, emphasis is placed on the common disorders of everyday practice, with very little discussion of the conditions encountered more rarely. In general the material is presented in a very straightforward and easily readable manner, and its value is further abetted by the inclusion of excellent photographic material and other illustrative material in the form of sketches, charts, and tables. Included also as an appendix are useful tables of drugs, diets, etc.

If one is interested in a complete discussion of the more unusual diseases, this book will fail to supply the necessary information; on the other hand, the included bibliographies are quite adequate. The place of this book in pediatric literature seems best defined in the editors' own words from the preface: "This book is planned to fit between the excellent volumes which serve as consultant texts for pediatricians and the well prepared small books of a more tabular style which have become available in recent years." Dr. Patterson and Dr. McCreary have done an outstanding job in the compilation of this up-to-date and practical text.

Kinderärztliche Notfallfibel: Abwehr akuter Lebensbedrohung. By B. de Rudder. Price, $3.95. Pp. 178, with 22 illustrations. Georg Thieme Verlag, Herdweg 63, (14a), Stuttgart N, 1956.

This book represents the German equivalent of the American "Handbook of Pediatric Medical Emergencies," by DeSanctis and collaborators, dealing with pediatric medical emergencies.

The book covers principal areas of pediatric medical emergencies, but it has notable major omissions. For example, the only acute poisoning covered is that due to mushrooms, while the huge area of poisoning due to inhalant and ingested toxins, drugs, and industrial products is left out. While concepts of rapid diagnosis are well presented, therapy is frequently outdated and, in some instances, unphysiological. The preoccupation of German pediatrics with baths, packs, and the use of fresh air harks back to many years ago, and much of the specific therapy recommended is more vigorous from the point of view of drug administration than American pediatricians are likely to sanction.

There are many reasons why this book will undoubtedly continue its present popularity in German-speaking medicine, but it has little to offer to the English-speaking reader.

Das Skelett des Kindes. By W. Swoboda. Price, $11.40. Pp. 184, with 199 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1956.

Dr. Swoboda has assembled in a small volume most of the radiologic information about the development, malformation, and disorders of the skeleton of the child. The volume is well organized, with 199 excellent illustrations.

The subjects of the opening sections on growth and maturation are not as adequately covered as those of the rest of the chapters. No mention is made of the well-established differences in the skeletal maturation of boys and girls, and in the graphs the ages at ossification of the epiphyses and round bones are not presented as separate standards for boys and for girls. One would have great difficulty in estimating "skeletal age" from these graphs. The data might better have been presentd in frequency distribution tables or at least as mean or median ages with standard deviation figures. The frequently used "Radiographic Atlas of Skeletal Development of the Hand and Wrist," by Greulich and Pyle, and the earlier "Todd Atlas" are not referred to.

Within the limitations of space, in subsequent chapters, the skeletal findings in abnormal states are well described and usually illustrated. As a reference book for the use of any physician who works with children, this should be a useful volume.

Discussions on Child Development. Edited by J. M. Tanner and Barbel Inhelder. Price, $10.00. Vol. 1, 240 pp., with 21 illustrations; Vol. 2, 271 pp., with 23 illustrations. International Universities Press, 227 W. 13th St., New York 11, 1957.

The lineage of the two conferences described in these volumes has been growing rapidly throughout the last ten years. In this country, a variety of meetings concerned with both the normal and the abnormal developmental behavior of infants, sponsored by the Macy Foundation and other groups, have paved the way for this type of discussion. The general series of Macy meetings set a pattern of bringing together members of many disciplines who might have knowledge bearing on a particular subject. In addition, a pattern of good reporting was established.

At the time of the termination of the Macy series on "Infancy and Childhood" (1947-1953) there began a similarly sponsored series of meetings on "Group Process" (1954-). It was evident that many of the participants at these latter meetings, where animal behavior and group psychology was being discussed, had knowledge in the field of child development that was of extreme importance. Coincidentally, an international seminar, "Mental Health and Infant Development," was held under the auspices of The World Federation for Mental Health in 1952. It is not, therefore, surprising that this present group, under the aegis of The World Health Organization, has met to further the study of "the biological, psychological and cultural factors in the development" of children.

Those present at the meetings described in these two volumes comprised a very distinguished group of persons from the fields of psychoanalysis, psychiatry, psychology, ethology, and a wide group of biological and physiological fields.

The presentations consist of a series of papers on various fields pertaining to human development. The genetics and physiology of growth, the electrical phenomena in the brain, and the cultural aspects of growth are all considered. The contributions of many centers were thus brought to bear on the important aspects of human relationships and the development of these between the child and his personal environment.

Of particular interest are the comments of the other guests on each paper, both as it proceeded and subsequent to its presentation. At times these comments become rather involved, but the editing is excellent, and it is possible to pursue the course of the conversations almost as well as if one were present. It offers to the reader a very graphic expression of erudite discussion, which is not usually obtained in the reading of papers. To many readers the discussions will have greater interest than the papers themselves.

The first volume consists of a series of presentations of various schools of thought on the development of the child. Beginning with physical development and a discussion of anencephalic growth, the papers proceed through a discussion of the criterion of the stages of development and the electroencephalographic development of children and conclude with psychoanalytic instinct theory and a cross cultural approach to child development problems.

During the second year all of these areas were amplified in a series of six further presentations. These are not entirely easy reading, but they are very well worth the study of any pediatrician concerned with the modern approach to developmental problems. Since the work of the pediatrician becomes more and more concerned with growth, development, and personality change, these volumes offer a very current approach, as seen by the very best people studying in the field. One suspects that further diffusion of knowledge in this field will continually come from groups such as this, where many people can contribute different points of view and thus enlarge the horizons of the practitioner in the area of growth.

BOOKS RECEIVED

Whitla's Dictionary of Medical Treatment. By R. S. Allison and T. H. Crozier. Ninth edition. Price, $10.50. Pp. 854, The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Psychotherapy of the Adolescent. By Benjamin Harris Balser. Price, $5.00. Pp. 270. International Universities Press, 227 W. 13th St., New York 11, 1957.

The Young Handicapped Child. By Agatha H. Bowley and L. Gardner. Price, $3.50. Pp. 127, with 35 illustrations. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Diabetes Mellitus. By T. S. Danowski. Price, $13.50. Pp. 510, with 26 figures and 26 tables. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Orthopedic Surgery in Infancy and Childhood. By Albert B. Ferguson Jr. Price, $15.00. Pp. 508, with 504 illustrations. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Clinical Toxicology of Commercial Products. By Marion N. Gleason, Robert E. Gosselin, and Harold C. Hodge. Price $16.00. Pp. 1160. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Lehrbuch der Kinderchirurgie. By M. Grob, M. Stockmann, and M. Bettex. Price, $32.40. Pp. 775, with 876 illustrations. Intercontinental Medical Book Corporation, New York 16, 1957.

Hutchison's Clinical Methods. By Donald Hunter and R. R. Bomford. Thirteenth edition. Price, $6.00. Pp. 452, with 95 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1957.

The Essentials of Paediatrics for Nurses. By I. Kessel. Price, $4.75. Pp. 213, with 88 illustrations. The Williams & Wilkins Company, Mt. Royal and Guilford Aves., Baltimore 2, 1957.

Calderwood's Orthopedic Nursing. By Carroll B. Larson and Marjorie Gould. Fourth edition. Price, $5.75. Pp. 701, with 307 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

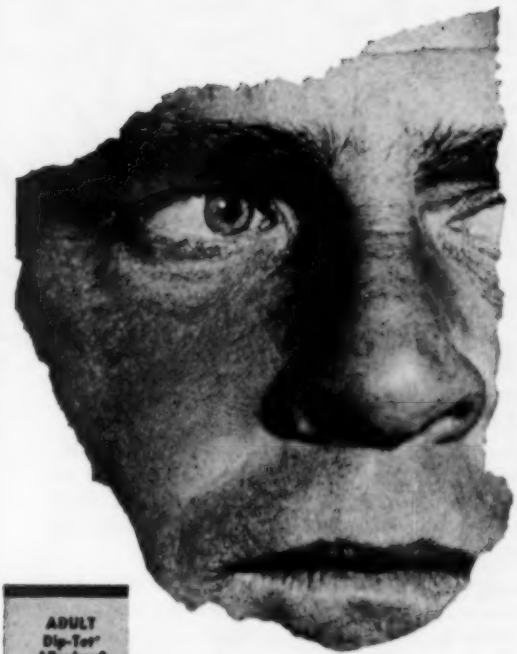
Medical Services for Rural Areas. By William A. Massie. Price, $1.25. Pp. 68, with 15 illustrations. Harvard University Press, 79 Garden St., Cambridge 38, Mass., 1957.

Ciba Collection of Medical Illustrations: Digestive System; Vol. 3, Pt. III. Liver, Biliary Tract and Pancreas. By Frank H. Netter. Price, $10.50. Pp. 165, with 133 illustrations. Ciba Pharmaceutical Products, Inc., 510 Morris Ave., Summit, N. J., 1957.

Mental Health Research Unit. By New York State, Department of Mental Hygiene. Price, not given. Pp. 127, with 34 tables. Syracuse University Press, Syracuse, N. Y., 1957.

Pathologie und Klinik der Cytomegalie. By G. Seifert and J. Oehme. Price, geb. DM 1960. Pp. 120, with 47 illustrations. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig, C. 1, 1957.

NEW TETANUS-DIPHTHERIA TOXOID PROTECTS PATIENTS 8 TO 80 WITHOUT SERIOUS REACTION



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[1] Edsall, Geoffrey: *Am. Jour. Public Health* 42:393-400, 1953.
[2] Long, E. P. and Sartwell, P. E.: *Bull. U.S. Army M. Dept.* 7:371-385, 1947.
[3] Editorial, *New England Jour. of Med.* 237:411-413, 1947.
[4] Edsall, Geoffrey; Altman, James S.; and Gaspar, Andrew J.: *Am. Jour. Public Health* 44:1537-1545, 1954.

For complete descriptive literature, dosage information, and a supply of wallet-sized immunization record cards for distribution to patients, write Dept. 36-J.

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These are the reasons, too, why oatmeal is widely recommended as the first solid food for the three-month-old infant's delicate digestive tract... and for the oldster whose changing dietary habits often make adequate protein nutrition difficult.

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Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

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THE NIPPLE THAT BREATHES

SEARER RUBBER CO., Akron 4, Ohio

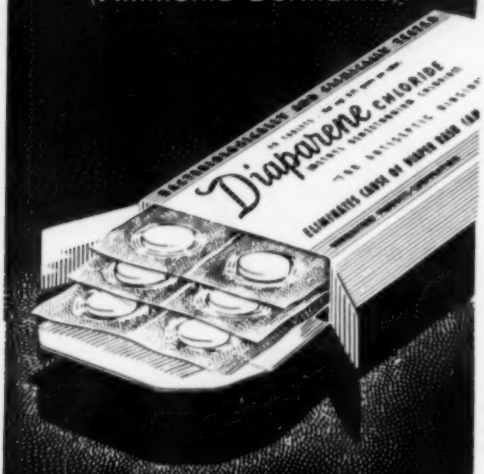
NIPPLES 10¢ NURSERS 25¢

Diaparene CHLORIDE

(METHYL BENZETHONIUM CHLORIDE)

ELIMINATES CAUSE OF DIAPER RASH

(Ammonia Dermatitis)



ANTISEPTIC DIAPER RINSE

Inhibits the formation of urinary ammonia in wet diapers up to 15 hours.

Benson, R.A. et al. J. Ped. 31 Oct. 1947

Supplied in packages of 20 and 40 tablets

PHARMACEUTICAL DIVISION
HOMEMAKERS' PRODUCTS CORPORATION
380 Second Avenue, New York 10, New York
36-48 Caledonia Road, Toronto 10, Canada

FOR NORMAL INTESTINAL FLORA

To promote the growth of favorable acid-producing microorganisms in the infant's intestine, SIMILAC provides both the appropriate carbohydrate and an appropriate fat.

SIMILAC:

(1) closely approximates breast milk in lactose content, which fosters the growth of gram-positive lactobacilli;

(2) by virtue of its corn oil, olive oil, coconut oil content, has been made comparable to breast milk in preponderance of unsaturated fatty acids, including the physiologically essential linoleic acid.

And to assure ease of digestion, SIMILAC fat globules are finely and uniformly homogenized. SIMILAC has the zero curd tension of breast milk.

Bibliographic references on request

SIMILAC®

there is no closer equivalent to the milk of healthy, well-nourished mothers

RESEARCH SERVICE Ross NUTRITION

ROSS LABORATORIES, Columbus 16, Ohio

For

CONSTIPATED BABIES AND CHILDREN

softens stools by dietary means—promotes aciduric intestinal flora

Malt Soup Extract promotes growth of favorable aciduric intestinal flora and provides mild peristaltic stimulation. Safe, effective, non-habit forming—as confirmed by medical literature and clinical use for over 45 years.

FOR INFANTS: A gentle laxative modifier of milk. Just add one or two tablespoonfuls routinely to the day's formula, or in water for breast-fed infants. Prompt results, even in stubborn cases.

FOR CHILDREN: One or two tablespoonfuls with breakfast and at bedtime, by spoon or in milk. Makes a delicious "malted" drink.

NOW 2 FORMS

* Specially processed non-diastatic barley malt extract neutralized with potassium carbonate.

LIQUID:
In 8 oz. and Pt. jars.

POWDER:
In 8 oz. and 16 oz. jars.
(use heaping measure)

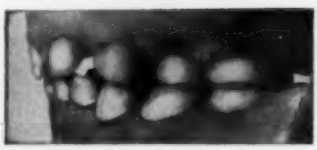
SEND FOR SAMPLES

BORCHERDT CO.

217 N. WOLCOTT AVE., CHICAGO 12, ILL.

THUMBSUCKING

since infancy caused this 4 year old's malocclusion.

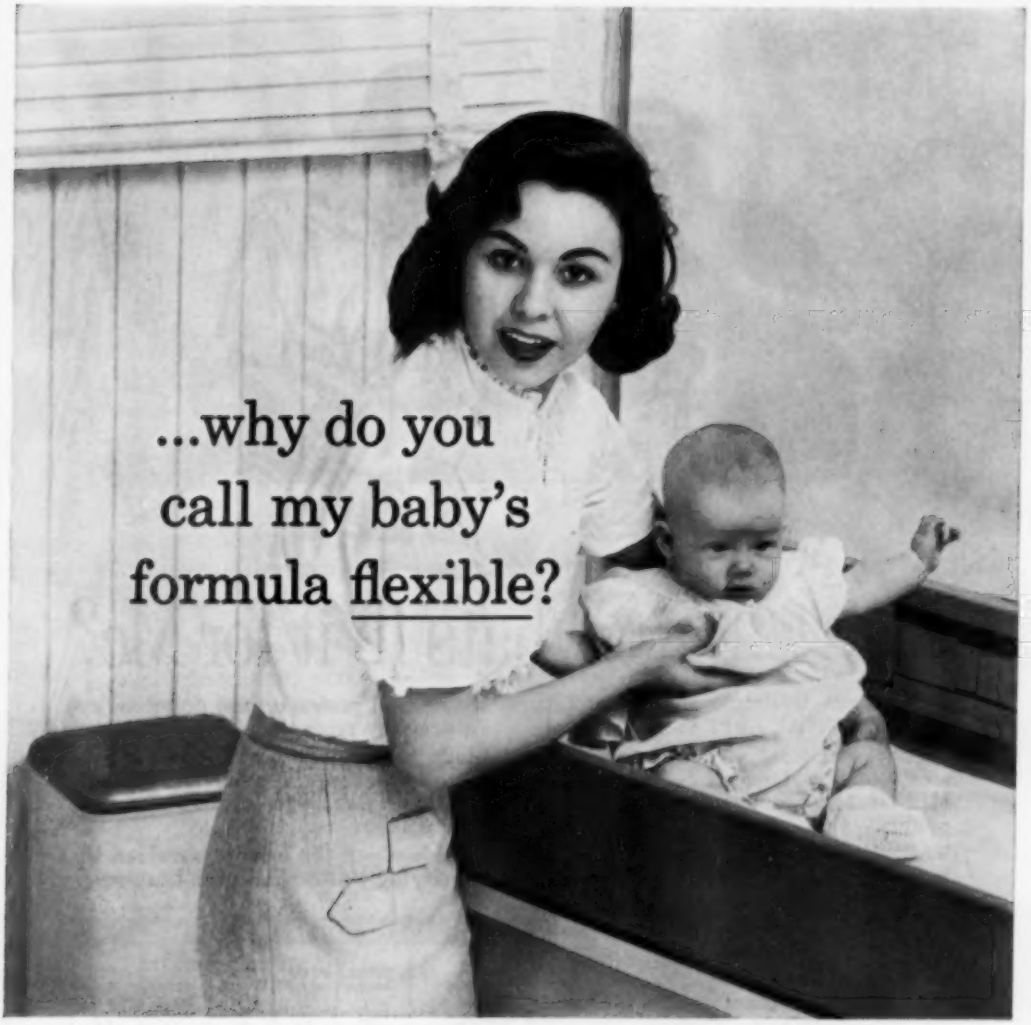


THUM
TRADE MARK

THUM broke the habit and teeth returned to normal position in 9 months.

THUM DISCOURAGES NAIL BITING TOO

GET THUM AT YOUR DRUGGIST OR SURGICAL DEALER.
PRESCRIBED BY PHYSICIANS FOR OVER 20 YEARS.



In contrast to proprietary formulas, which can only be made weaker or stronger, the evaporated milk formula is *flexible* because it can be:

– adjusted in dilution and *carbohydrate content* to meet neonatal needs without renal overload.

– gradually increased in concentration and the carbohydrate *specified by the physician* as the baby grows.

– adjusted in concentration, nutritional balance, or both, in any period of stress, such as illness.

– decreased in carbohydrate in direct ratio with the infant's increasing ability to assimilate solid foods.

– used in place of fresh milk at normal milk dilution during weaning from bottle to cup.

Carnation

"FROM CONTENTED COWS"

Optimum prescription-quality in today's trend to the individualized formula.

Doctor, Ask Yourself: What's in it for Me?

The answer is simple and important: PROFESSIONAL APPEAL!

"Mother pressure" is eliminated, pediatric control maintained, because VARAMEL is not promoted to the general public.

VARAMEL is made *exclusively* for infant feeding, advertised *exclusively* to the medical profession and promoted *exclusively* by professional representatives.

Study the analysis of VARAMEL . . . Compare its unique combination of modifications that builds sound, muscular, infants . . .

Double-check the results obtained by specifying VARAMEL in the hospital.

32 calories per fl. oz.

Furnished to hospitals without charge

SUGGESTED 24-HOUR FEEDINGS FOR FULL-TERM INFANTS

AGE	OUNCES VARAMEL	OUNCES WATER	(USE ONLY ONE) TBLS. DEX.-MALT.	(USE ONLY ONE) TBLS. CORN SYRUP	APPROX. CALS. PER OZ.
Newborn	10	14	1	½	14
2nd Week	13	15	2	1	17
3rd Week	13	13	3	1½	19
1 Month	13	13	4	2	20

Maximum Flexibility

Low in Cost

Simple to Use:

+ CARBOHYDRATE + WATER

Made entirely from Grade A Milk (U. S. Public Health Service Milk Code) modified by replacement of the milk fat with animal and vegetable fats and by the addition of vitamins and iron. No carbohydrate has been added.

Approximate Analysis

Protein	4.9%	Calcium	0.19
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

Calories per fl. oz., 32

Varamel

THE BAKER LABORATORIES, INC.

Milk Products Exclusively for the Medical Profession

MAIN OFFICE: CLEVELAND 3, OHIO
PLANT: EAST TROY, WISCONSIN

Meat...

and the Need for Adequate Protein in Therapeutic Nutrition

Liberal protein intake is considered to be of therapeutic value in a wide variety of pathologic conditions.[1] Advances in the understanding of protein metabolism indicate that dietary protein should provide amino acids in proportions paralleling physiologic needs.[2, 3] In experimental studies with animals, low protein diets supplying amino acids disproportionate to needs have been shown to effect physiologic harm by depressing growth, by inducing amino acid and B-vitamin deficiencies, and by causing deposition of fat in the liver.[4]

Hence not only the *amount* of protein but also its *quality* (in terms of its amino acid proportions) is important. It has been suggested[1] that for therapeutic purposes about two-thirds of the ingested protein come from foods of animal source, whose protein resembles human body protein in amino acid interrelationships. Depending on the needs of the patient, the therapeutic diet may supply 1.0 or more grams of protein per kilogram of body weight. Adequate caloric intake is required to protect the dietary protein from dissipation for energy purposes.

Meat, with its high content of top-quality protein, holds a prominent place among foods which supply this essential for establishing satisfactory levels of amino acids in physiologic proportions. It also contributes valuable amounts of B vitamins and essential minerals—nutrients which play a basic role in intermediate metabolism.

1. Proudfit, P. T., and Robinson, C. H.: Nutrition and Diet Therapy, ed. 11, New York, The Macmillan Company, 1955, pp. 314-320.
2. Harper, A. E.: Amino Acid Imbalance, Toxicities and Antagonisms, Nutrition Rev. *14*:225 (Aug.) 1956.
3. Amino Acid Requirements of Adult Man, Nutrition Rev. *14*:232 (Aug.) 1956.
4. Amino Acid Imbalance and Supplementation, Editorial, J.A.M.A. *161*:884 (June 30) 1956. Council on Foods and Nutrition, American Medical Association: Importance of Amino Acid Balance in Nutrition, J.A.M.A. *158*:655 (June 25) 1955.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

when sniffles hit the classroom

AND NASAL CONGESTION MAKES YOUNGSTERS MISERABLE

Neo-Synephrine®

Pediatric Nasal Spray

Contains Zephiran® chloride 1:5000, antibacterial wetting agent and preservative for greater efficiency

*Designed specifically for children**

Prompt and Prolonged Decongestion Sinus Drainage and Aeration

NO STING • NO SEDATION • NO EXCITATION

In practically all patients

Plastic Unbreakable Squeeze Bottle

Leakproof, Delivers a Fine Mist

*Also well suited for adults who prefer a mild spray.

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Neo-Synephrine (brand of phenylephrine) and Zephiran (brand of benzalkonium, as chloride, refined), trademarks reg. U.S. Pat. Off.